Tumour initiation, store-operated calcium entry (SOCE) and apoptosis: cyclic nucleotide dependence

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Abstract. Chemical instigators and modulators of tumourigenesis influence cell signal transduction pathways. Cyclic nucleotides and steroid hormones may contribute to the process of carcinogenesis or provide protection *via* apoptotic mechanisms. Although several pharmacologic classes of compounds influence cyclic nucleotide levels markedly, less is known about the class effects of promoters and blockers of tumourigenesis and apoptosis. This molecular modeling study uses cyclic nucleotide templates to investigate relative molecular similarity within compounds modulating tumourigenesis and apoptosis. Findings, in respect of superimposition and molecular fit of the investigated compounds, are related to their individual effects on cyclic nucleotide pharmacology. Modulators of tumourigenesis and estrogen receptor sub-type ligands relate to cyclic nucleotide structure. Estradiol and GPER ligands provide a similar pattern of fit to adenine nucleotide. Chemically diverse modulators of apoptosis, including K^+ channel ligands, fit to different components of cyclic nucleotide structure. Compounds modulating Ca^{2+} entry and IP3 receptors relate structurally to the nucleotide dioxaphosphinin moiety. Relative molecular similarity within the structures of apoptosis and tumourigenesis modulators identifies a unifying property within chemically disparate compounds. The ubiquitous generation of oxidative stress and ROS in cells by apoptosis modulating compounds may relate to the disruption of cyclic nucleotide regulated homeostasis mechanisms.

Key words: Cyclic nucleotides — Apoptosis — Tumourigenesis — SOCE

Introduction

Reliance on chemotherapy and radiation for cancer therapy is currently balanced by the aims of boosting natural immune defences and modulating tumour cell apoptosis/death mechanisms to the benefit of patients. Much of our knowledge of tumour initiation and development derives from the 2-stage animal model of carcinogenesis (Abel et al. 2009). In this model, simple chemicals introduced to epidermal cells have an opportunity to interact with cell membrane components and cytoplasmic signal transduction systems before reaching nuclear material. Potential targets of tumour initiators include cyclic nucleotides, kinases, phosphodiesterases (Saravani et al. 2012; Levin and Hammes 2016) ion channels and steroid receptors (Teisseyre et al. 2015; Levin and

Hammes 2016), in addition to compounds participating in the biochemical cascades prosecuting mitochondrial and cell surface death receptor pathways (Derakhshan et al. 2017).

Steroid hormones drive cell proliferation by activating nuclear receptors and the estrogen receptors that regulate G-proteins (GPER) (Capper et al. 2016; Feldman and Limbird 2017). GPER, linked to cancer progression and poor prognosis in breast cancer patients, facilitate rapid signaling *via* cell membrane receptors and ion channels (Prossnitz and Hathoway 2015; Machuki et al. 2018). Kow and Pfaff have reported on the complex targeting of all major categories of ion channel by estrogenic agents, their interaction with many signaling components and the likelihood of a common underlying mechanism (Kow and Pfaff 2018). Potassium channels represent the largest group of ion channels involved in cell proliferation and death events (Jehle et al. 2011; McFerrin et al. 2012; Ge et al. 2014; Teisseyre et al. 2015).

The NO/cGMP pathway influences cell calcium homeostasis markedly through processes involving voltage- and store-operated channels, IP3, ryanodine and calcium-sensing

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receptors (Watson et al. 1999; Greenberg et al. 2016). NO and cGMP also act independently to modulate capacitive Ca^{2+} entry (Watson et al. 1999), Ca^{2+} sequestration (Ishikawa et al. 2003) and Ca^{2+} loading of the sarcoplasmic reticulum (Bazan-Perkins 2012). cGMP has a dual action on Ca^{2+} entry in pancreatic acini, attributable to the Ca^{2+} sensitivity of NOS with respect to cytosolic and store Ca^{2+} (Xu et al. 1994). IP3 receptors link with extracellular signals and the phospholipase C pathway to facilitate the rapid passage of Ca^{2+} from endoplasmic reticulum to cytosol and stimulation of store-operated calcium entry (SOCE) (Thillaiappan et al. 2019). cGMP/PKG signaling regulates IP3R activity, promoting endoplasmic reticulum stress and apoptosis of cone photoreceptors in mice deficient in cyclic nucleotide-gated (CNG) channels (Ma et al. 2015). SOCE modulates malignant transformation and tumour progression, though the effects are inconsistent in different cell types and tumour stages (Xie et al. 2016). A functional link exists between endoplasmic reticulum distress, mitochondrial ROS production and damage to chemical and membrane infrastructure, that contributes to the milieu facilitating cell death (Redza-Dutordoir and Averill-Bates 2016).

The influences of cyclic nucleotides on apoptosis are inconsistent. Pro-apoptotic and anti-apoptotic properties of cAMP depend, to a considerable degree, on cell type (Insel et al. 2012). Intracellular cAMP receptors are amplified in breast cancer; protein kinase A (PKA) and EPAC, a guanine nucleotide exchange factor associated with PKA-independent responses, determine the fate of tumour cells (Kumar et al. 2017). Elevation of Jurkat cell cAMP potentiates apoptosis by enhancing cleavage of caspase-8 and augmenting the processing of Fas effector proteins (Naderi and Blomhoff 2008). In contrast, agents promoting cAMP formation in promonocytic leukemia cells attenuate the generation of apoptosis by etoposide (Garcia-Bermejo et al. 1998). One anti-apoptotic mechanism of cAMP involves the phosphorylation of pro-apoptotic proteins (Fatemi et al. 2015).

Guanylate cyclase activity and cGMP levels are abnormal in leukemic cells, lymphoid, ovarian and colorectal tumours (Orbo et al. 2007; Rappaport and Waldman 2018). Guanine nucleotide depletion and guanosine addition respectively induce and prevent apoptosis in neuroblastoma cell lines (Messina et al. 2004). Basal cGMP levels promote ovarian cancer cell survival by regulating p53 function (Fraser et al. 2006). Elevated cGMP and abnormal CNG channel expression results in photoreceptor oxidative stress and apoptosis in mouse retina (Sharma and Rohrer 2007; Wang et al. 2017). In neutrophils and breast cancer cell lines, PKG has a positive association with apoptosis (Brunetti et al. 2002; Fallahian et al. 2011; Saravani et al. 2012). However, estrogen-induced apoptosis of breast cancer epithelial cells is blocked by the NO/cGMP/PKG pathway (Kastrati et al. 2010). Tumour cell survival is also influenced by the concentration dependent effects of nitric oxide (NO). NO is protective for PC12 cells against the activation of caspase proteases and cell death but apoptotic for vascular smooth muscle cells (Kim et al. 2008).

As deregulation of cyclic nucleotide signaling is an early event in tumourigenesis, cell signal activation remains an active strategy for cancer prevention and treatment (Fajardo et al. 2014). One model of oncogenesis implicates nucleotide insufficiency in contributing to replication stress and genomic instability resulting from oncogene-induced cell proliferation (Bester et al. 2011). The assumption that the widely diverse chemicals initiating and promoting carcinogenesis have multiple targets need not be the case; rationalisation of their properties may simplify strategies of therapeutic intervention. cGMP and cAMP have well established roles as second messengers in cell signal transduction events. In terms of molecular structure, cyclic nucleotides could be considered as intermediate forms between receptor agonists, such as catecholamine hormones, and steroid structures. Molecular similarity provides some insight into mechanisms of signal transduction, particularly with regard to the potential of ligands to influence nucleotide conformational change This study uses a computational program to compare the molecular structures of cyclic nucleotides with tumour initiators, modulators of cell apoptosis and SOCE, to better understand processes underlying the initiation and suppression of carcinogenesis at the earliest stage.

Materials and Methods

The compounds of principle interest to this study are listed in Table 1. Molecular formulae of the compounds are from IUPHAR (Harding et al. 2018) and Pubchem (http://pubchem.ncbi.nlm.nih.gov) databases. Estrogen receptor subtype-selective ligands are reviewed by Paterni and co-authors (Paterni et al. 2014). The Nemesis software program (Oxford Molecular version 2.1) is used to build molecular structures from contents of the program fragment file and minimise structures by conformational analysis. The compound structures used for fitting are minimum energy conformers in an uncharged form. Anti-conformers of cAMP and cGMP are described by the torsion angle C8N9C1'O9 -33° (see Fig. 1). The computational program fits paired molecular structures on a three-point basis. The fitting points, comprised of atoms of similar type and partial charge within compound and nucleotide structures, are identified in the text with respect to nucleotide labels. Colour-coded atoms in the Figures identify ligand-fitting points: carbon – green, nitrogen – blue, oxygen – red, sulphur – yellow (see online version for color figures). To improve on presentation, bond order within the molecular structures is not shown and nucleotide structures are cropped. The Nemesis program computes goodness-of-fit values, in respect of inter-atomic distance at each fitting point and root mean square (RMS) value.

Table 1. Agents modulating apoptosis: reference sources and mechanisms

Compound	Induces apoptosis	Protects against apoptosis	Oxidative stress/ROS	cAMP	cGMP/NO
Arsenic trioxide	Chen et al. 2015	–	x	x	
Ascorbic acid	Lim et al. 2016	Witenberg et al. 1999	x		
Aspirin	Raza and John 2012	Jian et al. 2016	x		
BCNU	Yamaguchi et al. 2010	Petak et al. 1998			
camptothecin	Ha et al. 2009	–	x		
Carnosic acid	Zhang et al. 2017	Das et al. 2018	x		
Ceramide (C6)	Matsunaga et al. 2004	Agudo-Lopez et al. 2011	x		
Curcumin	Mortezaee et al. 2019	Benzer at al. 2018	x		x
Cyclopiazonic acid	Kang et al. 2011[1]	Harriman et al. 2002[2]	x		
Cytosine arabinoside	Kanno et al. 2004	–	x		
Dexamethasone	Deng et al. 2019	Ruiz et al. 2002	x		
Dichlorvos	Salem et al. 2016	–	x		
Dimethylbenzanthracene	Tsai-Turton et al. 2007	–	x		
Docosahexaenoic acid	Kang et al. 2010	Zhang et al. 2018	x		
Doxorubicin	Octavia et al. 2017	–	x		
17-β estradiol	Yang et al. 2017	Marathe et al. 2012			x
Folic acid	–	Octavia et al. 2017	x		
Gallic acid	Lin & Chen 2017	Chandrasrkhar et al. 2018	x		
Genistein	Lee & Park 2013	Luo et al., 2018	x	x	
Glucose	Zhang Y et al. 2019	–	x		
27-hydroxycholesterol	Marwarha et al 2017	Riendeau & Garenc 2009	x		
6-hydroxydopamine	Eftekhar-Vaghefi et al. 2015	–	x	x	
Isopimpinellin	Patil et al 2013	–			
α-Lipoic acid	–	Yang Y et al. 2012	x		
Methotrexate	AlBasher et al. 2019	–	x		
MNU	Emoto et al. 2016	–	x		
Nitric oxide	Bonavida & Garban 2015	Yoo et al. 2018	x		x
Nordihydroguaiaretic acid	Hernandez-Damian et al. 2014	Culver et al. 2005	x		
Palmitate	Kim et al. 2010	–	x		
Paxilline	Kang et al. 2011[1]	–	x		
Phytic acid	–	da Silva et al. 2019	x		
PMA	Itsumi et al. 2014	Bonavita et al. 2003			
pregnenolone	Xiao et al. 2014	Leskiewicz et al. 2008			
progesterone	Nguyen & Syed 2011	Cai et al. 2015	x		
Prostacyclin	Li et al. 2004	Pozner et al. 2005		x	
Quercetin	Lee et al. 2015	Suganya et al. 2018	x		x
Resveratrol	Gu et al. 2016	Lu et al. 2018	x		
Retinoic acid	Wang et al. 2014	Khafaga & El-Sayed 2018	x		
Silibinin	Ham et al. 2018	Yang et al. 2018	x		
Sulforaphane	Choi 2018	–	x		
Testosterone	Lopes et al. 2014	Kang et al. 2018	x		
Tetracaine	Lee et al. 2009	–	x		
Thapsigargin	Kang et al. 2011[1]	Harriman et al. 2002[2]	x		x
Vitamin A	Klamt et al 2008	Blomhoff 2004[3]	x		
Vitamin D	Koren et al. 2001	Shymanskyy et al. 2016	x		
Vitamin E	–	de Arriba et al. 2009	x		

BCNU, 1,3-bis(2-chloroethyl)-N-nitrosourea; DMBA, dimethylbenzanthracene; MNU, N-methyl-N-nitrosourea; PMA, phorbol myristate acetate; [1] compound sensitises cells to tumour necrosis factor-related apoptosis-induced ligand (TRAIL); [2] protection *via* nuclear receptor and transcription; [3] compound causes Ca^{2+} depletion prior to addition of toxicant.
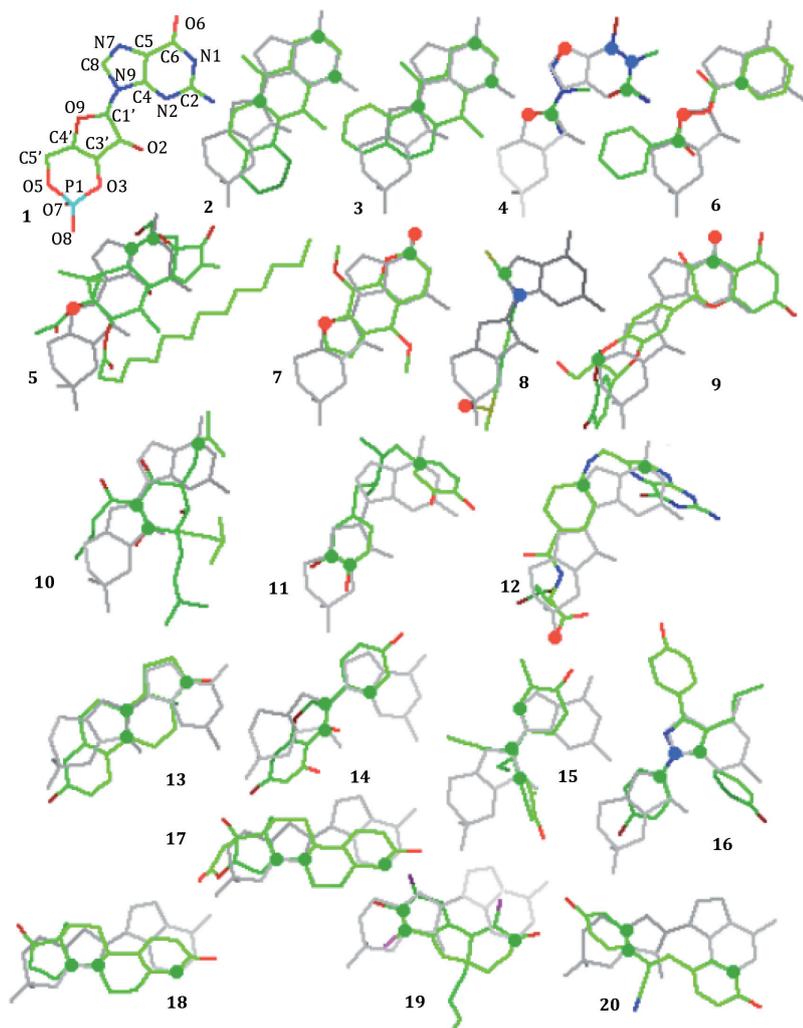
Figure 1. Tumour initiators, promoters and estrogen receptor (ER) ligands: fits to nucleotide structures (grey) cGMP (1-16), cAMP (17–20). (1) cyclic guanosine monophosphate (cGMP), (2 and 3) 7,12-dimethylbenz(a)anthracene (DMBA), (4) N-methyl-N-nitrosourea (MNU), (5) phorbol-12-myristate-13-acetate (PMA), (6) benzylperoxide, (7) isopimpinellin, (8) sulforaphane, (9) silibinin, (10) hexahydrocolupulone, (11) nordihydroguaiaretic acid, (12) folic acid, (13 and 18) estradiol, (14) genistein, (15) diphenylmethane derivative, (16) propylpyrazoletriol, (17) 16αLE, (19) SERM-βeta2, (20) (R)-DPN.

Results and Discussion

Tumour initiators and modulators

The dimethylbenzanthracene (DMBA) structure in Figure 1 (templates 2 and 3) approximates to the molecular size of cGMP (1) in contrast to the structure of the tumor promoter N-nitroso-N-methylurea (MNU) (4). The proportion of the nucleotide structure influenced by DMBA and MNU is made more equitable when two structures of MNU are superimposed on different regions of the nucleotide, as given in the Figure. MNU, phorbol myristate acetate (PMA) (5) and benzyl peroxide (6) structures are more similar to the nucleotide in their distribution of partial charge, in comparison to the carbon scaffold of DMBA. Isopimpinellin (7), sulforaphane (8) and silibinin (9), antagonists of tumour initiation and promotion, provide nucleotide O6 or O7 fitting points. Hexahydrocolupulone (10), nordihydroguaiaretic acid (11) and folic acid (12) protect

against skin changes in the mouse two-step skin carcinogenesis model (Hsu et al. 2013; Rahman et al. 2015; Koul et al. 2018).

A subtle difference of 2 amino acid residues within the ligand-binding receptor cavities of estrogen receptor subtypes ERα and ERβ limits the design of selective ligands (Paterni et al. 2014). A cAMP template is used for fitting ERβ agonist structures, as their effects are associated with the cAMP/PKA pathway (Wang et al. 2018). The agonists of ERα (13–16) and ERβ (17–20) provide two patterns of fit to the nucleotide structures. Estradiol (17β-estradiol) and ERα agonists fit to the imidazole moiety and ribose ring of cGMP. Estradiol and ERβ agonists fit to the aminopyrimidine moiety and ribose ring of cAMP. These fitting points contribute to different alignments of ERα and ERβ ligands on the nucleotide structures. Goodness of fit values are less than 0.16 Å (interatomic distance) and 0.0193 Å (RMS) for structures 1–12, and less than 0.16 Å (interatomic distance) and 0.0258 Å (RMS) for structures 13–20.

GPER receptor ligands

Estrogen modulation of cell cAMP and Ca^{2+} can be explained in terms of regulation at GPER receptors. Estrogen deficiency compromises the coupling of β-adrenergic receptors to G_s and G_i alpha proteins (Prossnitz and Hathaway 2015; Hou et al. 2018). On this account, an ATP template is used here to compare estrogen and GPER ligand structures (Fig. 2). The fitting points of potent and specific GPER agonists 1-[4-(6-bromobenzo[1,3)dioxol-5-yl)-3a,4,5,9b-tetrahydro-3H-cyclopentya[c]quinolin-8-yl)-ethanone (G1), GPER-L1 and GPER-L2, focus on the ribose ring (O3, C3') of ATP and linkage to the purine base (C1', N9, C4) whereas antagonists (4 and 5) fit solely to the purine base. The fits of agonist structures (1–3) introduce a cyclic ring or ring substituent in the vicinity of nucleotide O3, in contrast to the antagonists ethyl3-[5-(2-ethoxycarbonyl-1-methylvinyloxy)-1-methyl-1H-indol-3-yl)but-2-enoate (MIBE) (4) and 7-(quinoxalin-2-ylamino)-4H-benzo[b]pyrralo[1,2-d][1,4]oxazin-4-one (PBX-1) (5). Estradiol (6a-6l) provides many relevant fits to the ATP template with interatomic distance values in the range of 0.02 Å–0.18 Å (RMS values < 0.0333 Å). Alternative fits of estradiol, using C4 and C5 fitting points, or with fitting points located solely on the purine ring, are not given. Estradiol (templates 6a, 6b, 6c) completely or partially replicates the fits of the GPER agonist structures. This may have functional significance at receptor proteins, in the displacement or substitution of nucleotide. Steric hindrance in the region of nucleotide O2 and O3 hydroxyl groups may modulate the processing of ATP by adenyl cyclase. This potential for agonist-nucleotide interaction is represented here by the fits of the β-adrenergic receptor ligands isoprenaline (7) and R-O363 (8). The former structure has the potential to displace the nucleotide and promote cyclisation, whereas targeting of the O3 group involved in the cyclisation process by the antagonist may block the process. Template 6e gives an isoprenaline-like fit of estradiol.

The bonding region between nucleotide ribose and purine rings includes an intramolecular space defined by the torsion angle C2'C1'N9C4. This site is blocked by the fit of the
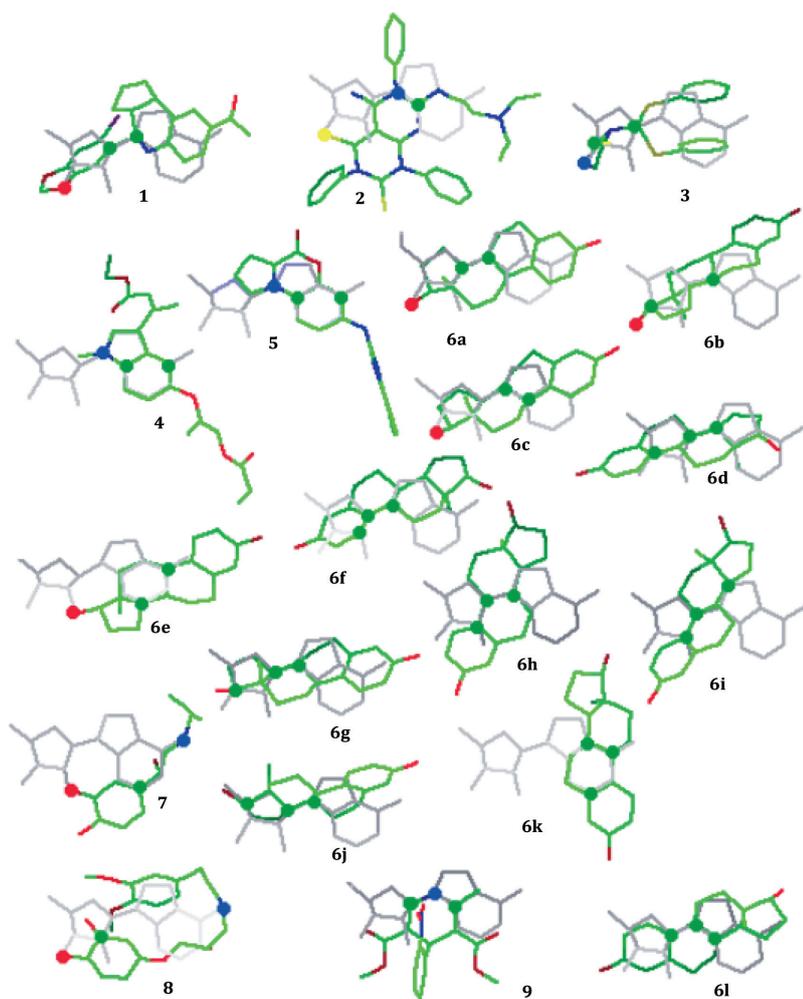

Figure 2. G-protein coupled estrogen receptor (GPER) ligands: fits to ATP (grey). (1) G1, (2) GPER-L1, (3) GPER-L2, (4) MIBE, (5) PBX-1, (6 a-l) estradiol, (7) isoprenaline, (8) Ro-363, (9) nifedipine.

calcium channel blocker nifedipine (9) and replicated by the fit of estradiol (6l). GPER agonist G1 opens the nifedipine sensitive L-type calcium channel in rat myometrium cells (Tica et al. 2011). GPER (GPR30) co-localise with other pharmacologic classes of G_α protein ligands, modulating serotonin and neuronal acetylcholine receptors (Xu et al. 2009; Hammond et al. 2011). Estrogen also modulates the strength of antinociception provided by opioid receptor agonists (Robinson et al. 2016). The estrogen templates 6b, 6f, 6g, 6h and 6j use fitting points common to ligands acting at acetylcholine, serotonin and opiate receptors (Williams 2018).

Modulators of apoptosis

Figure 3 gives a chemically diverse range of apoptosis modulating compounds providing good fits to the cGMP structure. The best of the alternative fits of testosterone (1 and 2) has nucleotide O6 and O7 fitting points. Nucleotide oxygens also contribute to the fits of dexamethasone (3), prostacyclin (6) and camptothecin (10). Nucleotide C6 is a common fitting point of various carbons in the structures of dexamethasone (3), pregnenolone (4), 27-hydroxycholesterol (5), doxorubicin (13), curcumin (14), carnosic acid (16), vitamin A (7), palmitate (8) and docosahexaenoic acid (9). Methotrexate (12) quercetin (15) and cytosine arabinoside (17) have some fitting points in common on the nucleotide guanine and ribose rings. Goodness of fit values of the structures in Figure 3 are less than 0.16 Å (interatomic distance) and 0.0250 Å (RMS).

The BK_{Ca} channel antagonists paxilline (1), progesterone (2) and genistein (3) fit across the length of the cGMP structure (Figure 4). Paxilline, in common with thapsigargin and cyclopiazonic acid, enhances apoptosis mediated by TRAIL (tumour necrosis factor-related apoptosis-induced ligand) and regulates the cell cycle of neuroblastoma cells (Kang et al. 2011; Maqoud et al. 2018). Progesterone and genistein induce apoptosis and protect against apoptosis (Table 1);
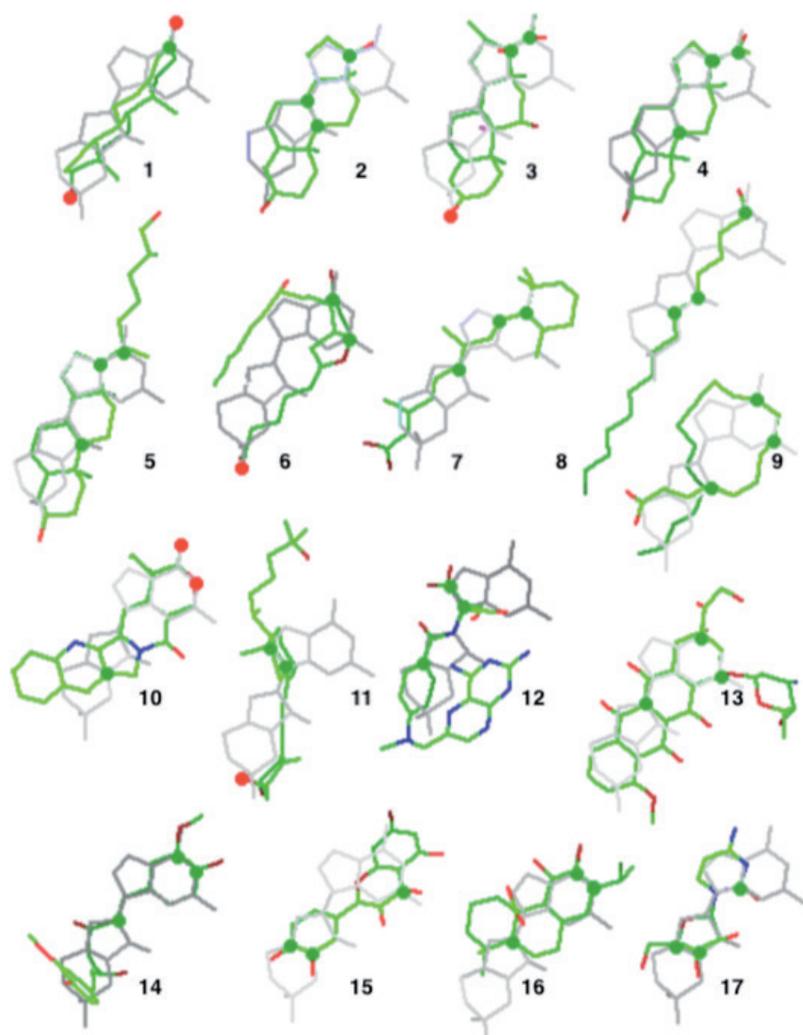

Figure 3. Compounds modulating apoptosis: fits to cGMP (grey). (1 and 2) testosterone, (3) dexamethasone, (4) pregnenolone, (5) 27-hydroxycholesterol, (6) prostacyclin, (7) all trans-retinoic acid, (8) palmitic acid, (9) docosahexaenoic acid, (10) camptothecin, (11) 1,25(OH)$_2$ vitamin D, (12) methotrexate, (13) doxorubicin, (14) curcumin, (15) quercetin, (16) carnosic acid, (17) cytosine arabinoside.
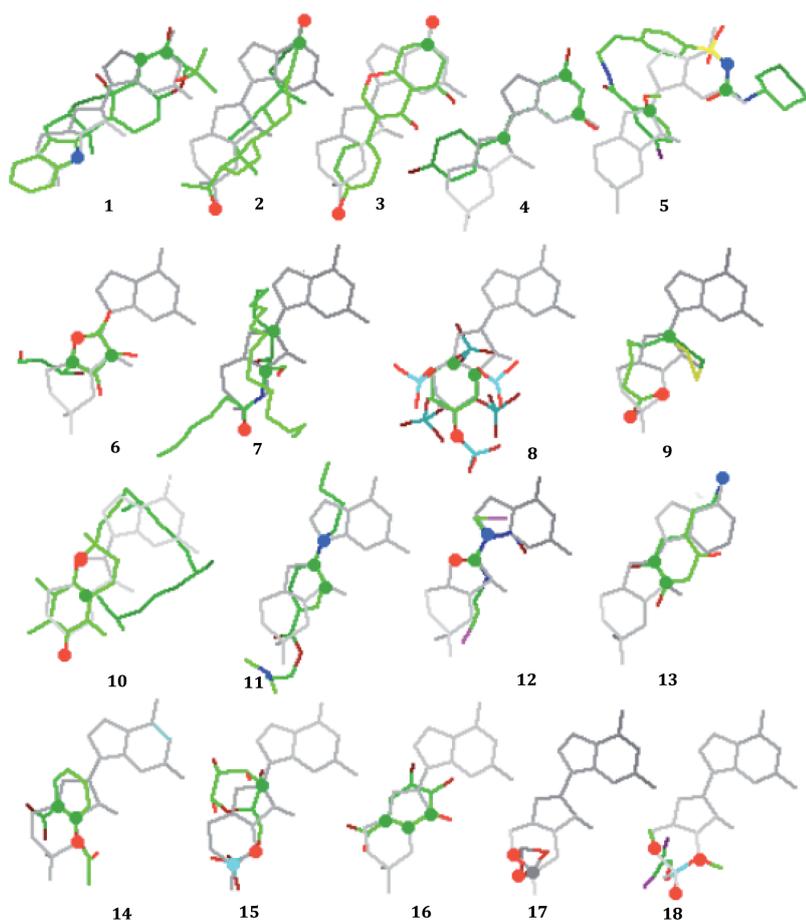
Figure 4. Compounds modulating apoptosis: fits to nucleotide structures (grey) cGMP or cAMP (13). (1) paxilline, (2) progesterone, (3) genistein, (4) resveratrol, (5) glibenclamide (6) ascorbic acid, (7) ceramide, (8) phytic acid, (9) α-lipoic acid, (10) vitamin E, (11) tetracaine, (12) BCNU, (13) 6-hydroxydopamine, (14) aspirin, (15) glucose-6-phosphate, (16) gallic acid, (17) arsenic trioxide, (18) dichlorvos.

both compounds have the same O6-O8 atomic distance, nucleotide fit and BK_{Ca} channel blocking activity. Resveratrol (4), an inhibitor of Kv and K_{ATP} channels, stimulates insulin secretion (Chen et al. 2007) and displaces the K_{ATP} channel antagonist glibenclamide (5) from the sulphonylurea receptor (Hambrock et al. 2007).

Figure 4 (6–18) also introduces a group of oxygen rich compounds with apoptosis modulating properties and a more restricted fit to the cGMP structure. Ascorbic acid (6) provides an alternative fit (not shown) based on the fitting points of 1,3-bis(2-chloroethyl)-N-nitrosourea (BCNU) (12). Ceramide (7), α-lipoic acid (9), vitamin E (10), glucose-6-phosphate (15) and gallic acid (16) have fitting points on the nucleotide phosphobicyclic ring. The fits of phytic acid (8), aspirin (14), arsenic trioxide (17) and dichlorvos (18) to the terminal cyclised ring are more restricted. Lipoic acid inhibits apoptosis caused by high glucose levels in cell culture (Yang et al. 2012). Phosphorylation of glucose to glucose-6-phosphate is an initial step in glucose utilisation and up-regulation of glucose-6-phosphate dehydrogenase promotes β-cell apoptosis (Lee et al. 2011). Arsenic trioxide influences cell Ca^{2+} by inhibiting the IP3 receptor

and sarcoplasmic reticulum Ca^{2+} ATPase (Hsu et al. 2012; Zhang et al. 2016). The structures of dichlorvos and arsenic trioxide provide the minimum and maximum goodness of fit values of compounds given in Figure 4: interatomic distance values < 0.05 Å and < 0.18 Å, RMS 0.0028 Å and 0.0347 Å, respectively. The fit of the apoptosis-inducing agent 6-hydroxydopamine (13) is to adenine cyclic nucleotide.

There is considerable interaction between the above compounds in cell cultures. Arsenic trioxide induced apoptosis is enhanced by ascorbate, docosahexaenoic acid, genistein, quercetin, retinoic acid (Michel et al. 2003; Baumgartner et al. 2004; Sanchez et al. 2009; Shen et al. 2012; Wei et al. 2014) and ameliorated by resveratrol (Chen et al. 2015). cAMP prevents apoptosis induction by palmitate, docosahexaenoic acid, arsenic trioxide and doxorubicin, in different cell lines, by promoting phosphorylation of PKA target proteins and the cAMP-GEF pathway (Kwon et al. 2004; Miura et al. 2005; Safa et al. 2014; Fatemi et al. 2015). 6-Hydroxydopamine induced apoptosis is reduced by NO, cAMP, curcumin, phytic acid and gallic acid (Ha et al. 2003; Fujita et al. 2006; Jaisin et al. 2011; Xu et al. 2011; Chandrasekhar et al. 2018). Vitamin E blocks apoptosis induction by 7-β-hydroxycholesterol

and docosahexaenoic acid in human cell lines (Lyons et al. 2001; Xiong et al. 2012). Quercetin protects against methotrexate and dichlorvos induced oxidative stress and apoptosis in rats and HCT116 cells, respectively (Erboga et al. 2015; Salem 2016). Camptothecin induced apoptosis is enhanced by aspirin and inhibited by dexamethasone (Alfonso et al. 2009; Qian et al. 2009). Retinoate augments or synergises with the actions of 8-Cl-cAMP, carnosic acid and vitamin D in the growth inhibition or apoptosis of cancer cells (Srivastava et al. 2000; Steiner et al. 2001; Sha et al. 2013). Vitamins A and D induce resistance to apoptosis promoted by idarubicin, an analogue of doxorubicin (Ketley et al. 1997). Apoptosis and cardiotoxicity resulting from doxorubicin is reduced by curcumin *via* attenuation of mediator and enzyme activity, including iNOS (Benzer et al. 2018). Cytosine arabinoside mimics the neuroprotective action of cAMP on dopaminergic neurons (Mourlevat et al. 2003). One property unifying these disparate compounds is their relative molecular similarity to cyclic nucleotide structure, identified in Figures 3 and 4. Several of the above interactive compounds share fitting points and/or superimpose on the nucleotide structures with similar fits.

Table 1 lists the above compounds with established apoptosis modulating properties *via* effects on second messengers and oxidative stress/ROS mechanisms. That so many of these compounds both induce and inhibit apoptosis, by similar mechanisms in different cell types, is surprising. In megakaryocytes, for example, prostacyclin induced cAMP antagonises apoptosis promoted by NO (Pozner et al. 2005), yet prostacyclin induced cAMP in VSMC cells initiates apoptosis (Li et al. 2004). Arsenic trioxide also promotes cAMP generation (Abudoureyimu and Muhemaitibake 2017) although, unlike the adenyl cyclase stimulating properties of epinephrine, forskolin and prostacyclin, the mechanism is obscure. The anti-apoptotic effects of estradiol and quercetin, on osteocytes and pancreatic β-cells respectively, are NO/cGMP mediated; cGMP mimicking the effects of estradiol on osteocytes (Marathe et al. 2012; Suganya et al. 2018). In a breast epithelial cell line, NO/cGMP signaling blocks estradiol induced apoptosis (Kastrati et al. 2010).
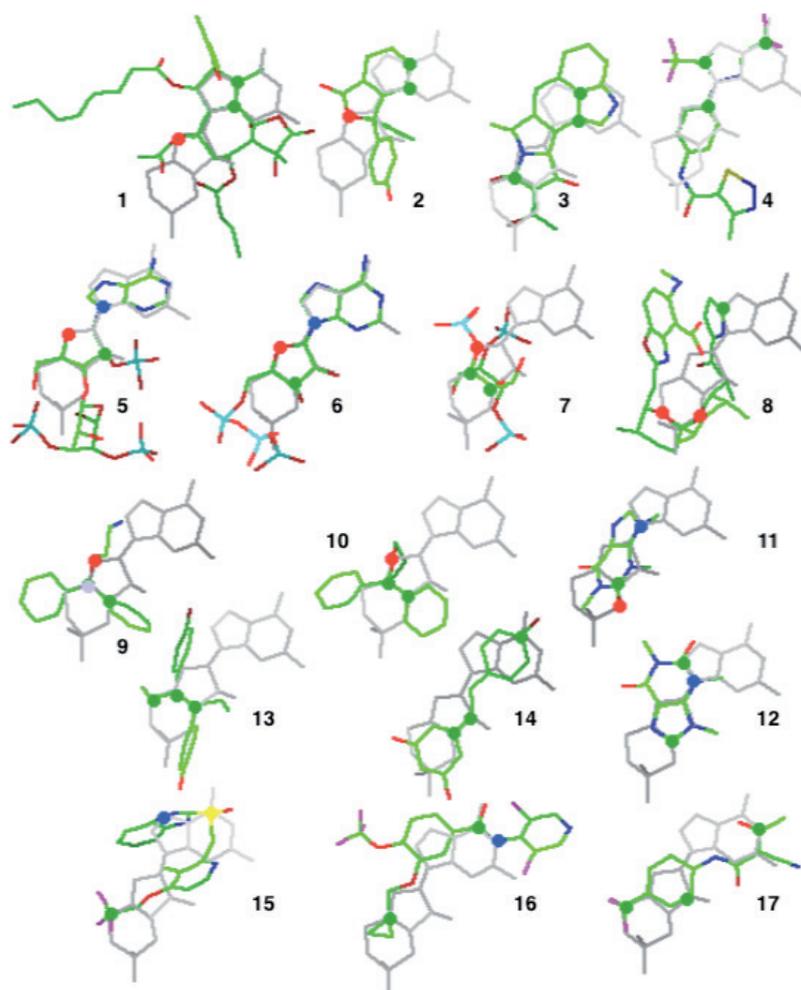

Figure 5. Compounds modulating store-operated calcium entry (SOCE): fits to cGMP (grey). (1) thapsigargin, (2) phenolphthalein, (3) cyclopiazonic acid, (4) BTP2, (5) adenophostin, (6) ATP, (7) inositol triphosphate, (8) A23187, (9) 2-aminoethoxydiphenylborane (2-APB), (10) diphenylfuranhydantoin, (11), (12) caffeine, (13) diethylstibestrol, (14) resveratrol; (15) lansoprasole, (16) roflumilast, (17) teriflunomide.

Nitric oxide displays a dual role in apoptosis regulation; low concentrations protect cells, whereas excessive levels cause apoptosis (Mori 2007). In retrospect, it is of interest to note that the cGMP-based molecular similarity of tumour modulating structures (Fig. 1) is associated with apoptosis; DMBA, MNU and PMA induce apoptosis (Table 1). Apoptotic and anti-apoptotic actions have been observed for gallic acid, genistein, silibinin and nordihydroguaiaretic acid, whereas folic acid is anti-apoptotic.

Ca^{2+} store modulators

Thapsigargin (Fig. 5) (1) and cyclopiazonic acid (3), inhibitors of ER Ca^{2+} ATPase and release agents of the Ca^{2+} store, provide similar fits to the guanine and ribose rings of cGMP. This molecular similarity within the structures of thapsigargin, cyclopiazonic acid and cGMP is also functionally relevant. Cell death and apoptosis are associated with sustained increases in cGMP and cytosolic Ca^{2+} (Yoshida et al. 2006; Sharma and Rohrer 2007; Nimmervoll et al. 2009). cGMP inhibits the actions of cyclopiazonic acid and thapsigargin on SOCE; particulate and soluble guanylyl cyclases serve distinct regulatory roles in this process (Kwan et al. 2000; Zolle et al. 2000). Estradiol and genistein attenuate apoptosis induced by thapsigargin in primary cortical neurons (Linford and Dorsa 2002).

The nucleotide fitting points of IP3 (7) and the IP3R agonists adenophostin (5) and ATP (6) focus on the nucleotide ribose ring. The aforementioned compounds reveal a similar distribution of oxygen-rich groups in relation to the structure of cGMP. The phosphorylated pyranose ring of adenophostin, the triphosphate chain of ATP, and carbonyl residues of thapsigargin and cyclopiazonic acid enclose the dioxaphosphinin ring of cGMP. This distribution of chemical groups is absent in the thapsigargin inhibitors phenolphthalein (2) and BTP2 (4). The dioxaphosphinin ring is also relevant to the fits of calcium ionophore A23187 (8), SOCE channel inhibitors 2-APB (9) and diphenylfuranhydantoin (10), and caffeine. Caffeine (11 and 12) provides at least 2 fits to the cyclic nucleotide structure. Template 11 represents a potential blocking action of caffeine on the dioxaphosphinin ring targeted by IP3 agonists. In addition to inhibiting IP3 receptors, caffeine and 2-APB deplete the Ca^{2+} store in a similar manner to thapsigargin (Saleem et al. 2014; Huang et al. 2017). In mouse smooth muscle cells, cGMP abolishes a sustained non-selective cation current activated by caffeine following calcium store depletion (Wayman et al. 1996).

Compounds with a stilbene pharmacophore, notably diethylstilbestrol (13), inhibit thrombin-induced Ca^{2+} release from platelet ER and thapsigargin-induced Ca^{2+} influx (Dobrydneva et al. 2003). Blockage of IP3-sensitive Ca^{2+} release and SOCE is attributed to the alkyl side-chains of diethylstilbestrol as genistein and resveratrol, structures

without these substituents, only inhibit platelet Ca^{2+} influx (Dobrydneva et al. 2003, 2010). Alkyl side-chains cannot be used as nucleotide fitting points for the resveratrol structure (14). Aromatic rings within the structure of 2-APB (9) replace the carbonyl and phosphate groups of IP3 agonists, giving the antagonist less potent activity in regard to SOCE (Rahman and Rahman 2017). The nucleotide fits of more recently developed inhibitors, lansoprazole, roflumilast and teriflunomide (15–17) (Rahman and Rahman 2017) impact the nucleotide dioxaphosphinin ring with cyclopropane or trifluoride residues. Aspirin (Fig. 4, (14)) and salicylate may also inhibit tumour cell growth by targeting SOCE (Villalobos et al. 2017).

Although the Ca^{2+} modulating agents listed in Table 1 have a dual action, in contrast to resveratrol the protective actions of thapsigargin and cyclopiazonic acid involve transcription. Resveratrol enhances palmitate-induced ER stress and apoptosis in some cancer cell lines but attenuates apoptosis induced by high levels of glucose and palmitate in cardiac myoblast cells (Rojas et al. 2014; Xu et al. 2018). Estradiol blocks resveratrol-induced apoptosis in MCF-7 breast cancer cells (Zhang et al. 2004). Cyclopiazonic acid increases apoptosis in insulin-secreting cells (Zhou et al. 1998). Apoptosis in cancer cell lines is promoted by diethylstilbestrol, A23187, teriflunomide, lanzoprazole and caffeine (Robertson et al. 1996; Kajitani et al. 2007; Hail et al. 2012; Zhang et al. 2014; Liu et al. 2017). The IP3 receptor mediates the apoptotic action of sulforaphane (Hudecova et al. 2016). Goodness of fit values of the structures given in Figure 5 are less than 0.16 Å (interatomic distance) and 0.0311 Å (RMS).

The capacity of compounds to cause apoptosis and also provide protection against the process generates a confusing picture. The majority of these data relate to cell culture studies which may have methodological weaknesses: the use of pharmacological rather than physiological levels of compounds; the dual and concentration dependent actions of agents such as NO and ROS; culture systems deficient in sterol, steroid and nucleotide compounds that have the potential to change test outcomes. This difficulty in replicating the tissue environment is imposed on the natural differences in signal transduction pathways operating in various cell types. Imbalances in cyclic nucleotide cross-talk signaling networks initiate pathogenesis (Zhao et al. 2017). Effector proteins regulated by cGMP and cAMP show little selectivity at some cyclic nucleotide binding domains; selectivity requires the differential recognition of amino and carbonyl groups at adenine C6, and guanine C6 and C2 (Campbell et al. 2016). Compounds with the capacity to displace or substitute cyclic nucleotides from their receptors are potential disruptors of cell physiology.

The study findings explain how initiators/modulators of tumourigenesis, apoptosis and ion channel activity may

disrupt the regulation of cell function by cyclic nucleotides. Although the investigated compounds vary in molecular size and chemical diversity, their relative molecular similarity to cyclic nucleotide structure is a unifying characteristic. Some endogenous structures (dexamethasone, testosterone, PgI2) relate structurally to the complete nucleotide axis, whereas other natural (vitamins A and D) and pharmaceutical (methotrexate, cytosine arabinoside) compounds do so partly. Compounds modulating $Ca^{2+}[i]$ *via* IP3 channels and SOCE demonstrate structural characteristics that relate to the nucleotide dioxaphosphinin ring. Compounds with a record of protection against apoptosis (folic acid, vitamin E, α-lipoic acid, phytic acid) provide non-specific fits to cyclic nucleotide dioxaphosphinin rings, although this type of fit is also given by apoptosis-inducing glucose-6-phosphate and ceramide (C6) structures. Molecular similarity within smaller structures (arsenic trioxide, dichlorvos) is limited to the terminal region of the cyclised ring, implicating this nucleotide moiety as one relevant to the modulation of ROS and oxidative stress.

In summary, this study provides novel data in respect of the molecular structures of compounds with established transformative and protective actions on cells, and supporting evidence for the role of cyclic nucleotides in determining the health of cells.

Molecular similarity within the compound structures is indicative of the critical role of cyclic nucleotide binding domains in the physiologic processes of tumourigenesis and apoptosis. Nucleotides and steroid hormones represent a first line of chemical defence against initiators/modulators of carcinogenesis and apoptosis, rendering cells susceptible to imbalances.

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