Electronic supplementary information (ESI) for *Natural Product Reports*

SUPPORTING INFORMATION

Coumarin heterocyclic derivatives: chemical synthesis and biological activity.

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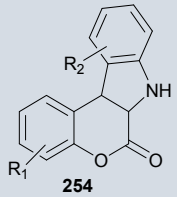
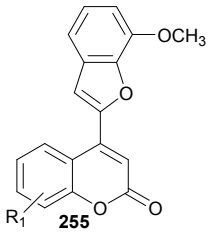
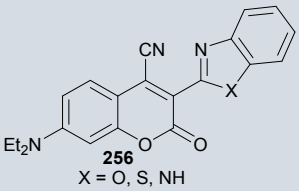
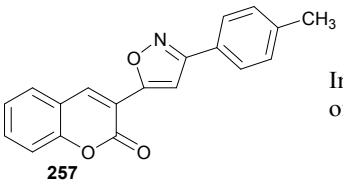
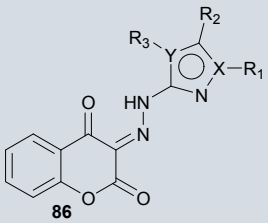
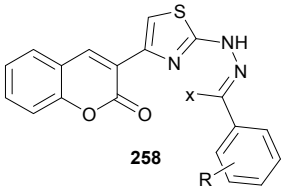
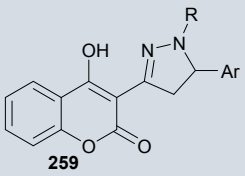
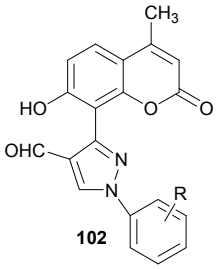
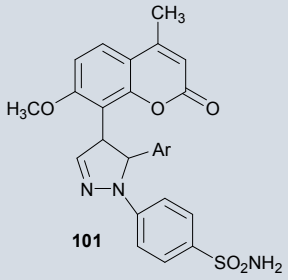
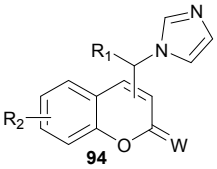
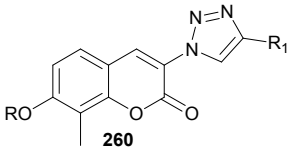
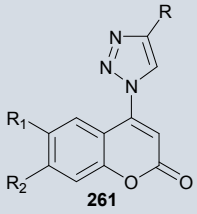
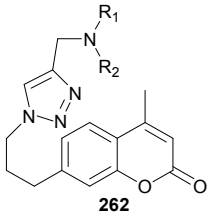
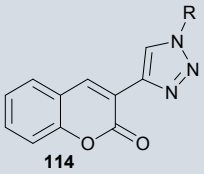
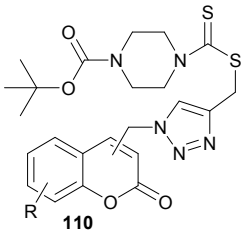
The 'Supporting Information' is a supplementary data illustrating a summary of all the available biological activities for the discussed coumarin heterocyclic derivatives.

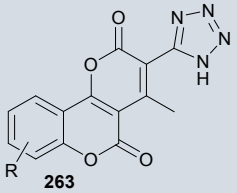
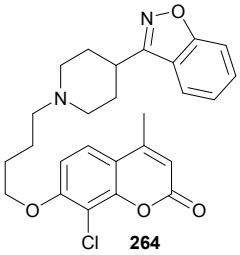
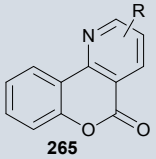
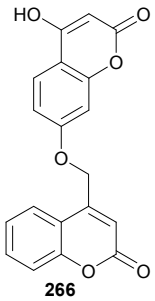
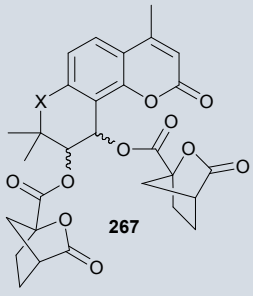
The 'Supporting Information' was composed of two parts:

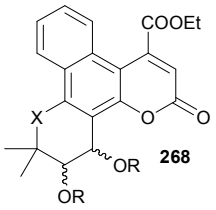
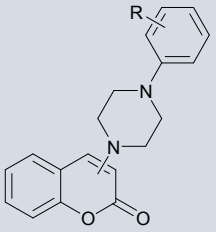
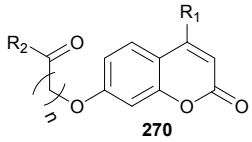
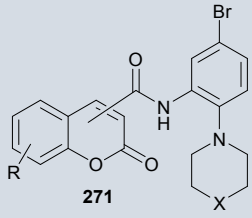
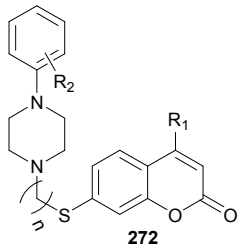
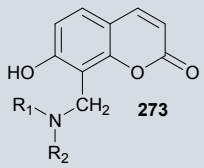
1. **Table S1**. Summary of the bioactivity data of the heterocyclic coumarin derivatives
2. **References**

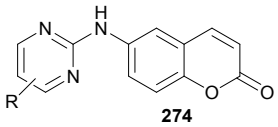
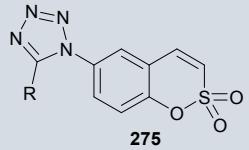
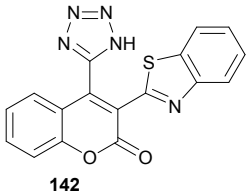
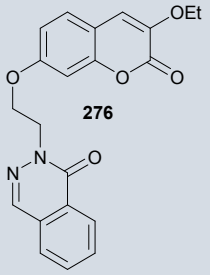
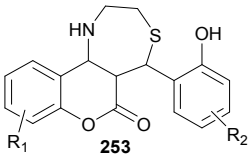
Compound	Activity	Potency of the most active derivative	Comments	Ref.
Pyrrole, indol and isoindole				
 254	Inhibitors of DYRK1A kinase	IC_{50} = 0.067 μM	Potent kinase and topoisomerase I inhibition: (a) The C-3 and C-10 bis hydroxylated chomenoindole exhibited strong topoisomerase I inhibition (IC_{50} = 38.5 μM) with only a weak sub-nanomolar kinase effect; (b) when a hydroxy group is positioned in C-2, an selective DYRK1A inhibition was observed (IC_{50} = 0.067-0.076 μM). Molecular modelling docking studies revealed a Lamellarin-like binding mode with the ATP active site.	1
Furane, benzofurane and thiophene				
 255	Anti-inflammatory (Carrageenin-induced hind-paw oedema)	% inhibition Oedema volume at 1h = 84%	Inhibition of inflammation comparable with phenylbutazone	2
Imidazole, oxazole, isoxazole, thiazol				
 256 X = O, S, NH	Cytotoxic towards human cancer cell lines	Cell line / IC_{50} (μM) U87 0.21 B16 1.3 HeLa 1.2 DLD-1 0.21 SiHa 2.0 NIH 3T3 2.8		3
 257	Inhibited the invasion of MCF-7/6 cells	IC_{50} = 1 μM.	The compounds inhibited only invasion without affecting growth, which excludes that they due their activity to cytotoxicity The mechanisms of action are not elucidated	4
 86	Cytotoxic and apoptogenic effect towards human cancer cell lines	Cell line / IC_{50} (μM) MCF-7 100-200 PC-3U87 100-200 MDA-MB231 20-60 LNCaP 20-60 U937 20-60	The effects were cancer cell line dependent. MDA-MB-231, LNCaP and U937 cells were most sensitive, MCF-7 were less sensitive, and PC-3 cells were more resistant Pro-apoptotic effect A sulfur in position 3 of the five membered heterocycle increased the effect on cell viability	5
 258	*In vitro* antimicrobial activity against *S. aureus, S. pyogenes, H. influenzae, C. albicans, M. tuberculosis*	MIC (μM) = 15-663	The antimicrobial activity was enhanced by bromide and hydroxyl groups. A hydroxyl group at the ortho position of a benzylidene imine was more effective than meta and para substitution patterns.	6

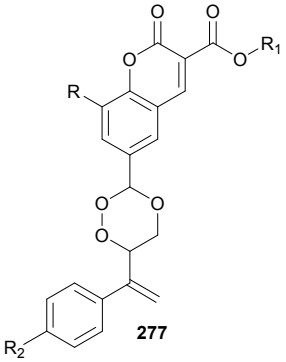
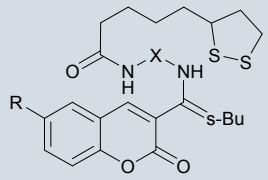
Imidazole, pyrazole				
 **259**	Anticoagulant activity [*in vivo* coagulation time (CT) and prothrombin time (PT) determination; *in vitro* measurement of PIVKA-II levels]	Relative potency (%) compared to warfarin (R.P. %) = 17.3-19.4% CT = 20.83-22.50 s PT = 3.373-4.017 min	Anticoagulant activity: modest to high activity compared to warfarin Activity increased by introduction of acetyl or phenyl group at position 1 of the pyrazolyl functionality Ambiguity between *in vitro* (low) and *in vivo* (high), attributed to their *in vivo* dual mechanism of action of coumarin and pyrazole pharmacophore group	7
 **102**	Antibacterial: *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa* Antifungic: C. *neoformans*, *A. niger*, *A. flavus*, *C. albicans* Antioxidant (DPPH)	Moderate to relatively strong Moderate to relatively strong Poor radical scavenging ability at lower concentrations.	Compounds with chloro exhibited remarkable activity against all the organisms tested.	8
 **101**	Cytotoxic and apoptogenic effect towards human cancer cell lines (60 cancer cell lines according to US NCI protocol)	The tested compounds exhibited high potency against colorectal cell line HCT-116 IC_{50} = 0.01-2.8 μM	More potent than doxorubicin (IC_{50} of Doxorubicin = 0.63 μM) Potential molecular target PI3K (p110α/p85α)	9
 **94**	Inhibitors of aromatase, assayed against AR (CYP19) and 17α-hydroxylase/C17,20-lyase (CYP17), two related P450 enzymes, which are responsible for catalyzing the final step in estrogen and androgen biosynthesis, respectively	IC_{50} = 0.047 μM (363-fold more active than aminoglutethimide)	The most salient features from the SAFIR: (a) The position of the 1-methylimidazolyl substituent on the coumarin ring plays a central role in the modulation of the inhibitory activity (b) The length of the bridge linking the imidazole to the coumarin ring was another important structural element modulating the enzyme affinity (c) A single CH_2 seems to be an optimal bridge to link the imidazolyl to the coumarin ring (d) The effect on the affinity obtained by introducing a phenyl substituent in the coumarin scaffold is position-dependent. (e) The carbonyl group of the coumarin lactone ring seems an important structural determinant for the activity since the thiocarbonyl is significantly less active	10

 **95**	Inhibitors of human carbonic anhydrase (hCA) I and II.	IC_{50} = 22.09 μM and 20.33 μM for hCA I and hCA II, respectively.	All the synthesized compounds inhibited the CA isoenzymes activity	11
Triazole				
 **260**	Cytotoxic towards human cancer cell lines	Cell line / IC_{50} (μM) MCF-7 / 7.45-18.33 SKBr-3 / 6.52-8.17	Its anti-proliferative activities are directly related to Hsp90 inhibition These compounds are interfering with the Hsp90-mediated protein folding process	12
 **261**	Cytotoxic towards human cancer cell lines	Cell line / IC_{50} (μM) MCF-7 / 5.89 SW480 / 1.99 A549 / 0.52	The compounds inhibit the proliferation of cancer cells through inducing apoptosis and arresting the cell-cycle at G2/M phase	13
 **262**	Antifungal: *A. niger*, *A. fumigatus*, *A. flavus*, *C. albicans* Antibacterial: *S. aureus, B. subtilis, S. epidermis, E. coli, P. aeruginosa, S. typhi, K. pneumoniae*	Strong Strong	Low or moderate toxicity risks in in silico analysis Good oral bioavailability Druglikeness and drug-score values similar or better than some commercial antimicrobials such as amphotericin B.	14
 **114**	Inhibitors of inducible nitric oxide synthase. The secretion of tumor necrosis factor (TNF-α), prostaglandin E2 (PGE2) and the production of NO by neutrophils were quantified in basal or *Escherichia coli* lipopolysaccharide (LPS)-stimulated conditions.	Most of compounds significantly inhibited NO production by LPS-stimulated neutrophils with a concentration of 10 μM None of the tested molecules inhibited the secretion of PGE2 and TNF-α.	This compounds reduced nitric oxide (NO) production by reducing iNOS gene and protein expressions and iNOS activity. Compounds did not affect eNOS activity,	15
 **110**	Inhibitors of lysine specific demethylase 1 (LSD1) The downregulation of LSD1 expression or inhibition of its activity can inhibit cancer progression	IC_{50} = 0.39 μM 74-fold more potent than that of tranylcypromine	Reversible inhibition *In vitro* selectivity against lysine specific demethylase 1 without inhibition against monoamine oxidases (MAOs) A and B Most of the mono-substituted coumarins at the 7-position had excellent inhibitory activity	16
Tetrazole				

 **263**	Antibacterial: *S.aureus, S.typhi, E.coli*	Minimum inhibition concentration (MIC) Moderate to relatively strong		17
Pyridine				
 **264**	Antipsychotics. Affinities of different amine moieties for dopamine D_2, and serotonin 5-HT_{1A}, and 5-HT_{2A} receptors	Receptor affinity Ki 0.0026 μM (D_2) 0.0033 μM (5-HT_{1A}) 0.0003 μM (5-HT_{2A})	High affinity for dopamine D_2 and D_3, and serotonin 5-HT_{1A} and 5-HT_{2A} receptors. Low affinity for 5-HT_{2C} and H1 receptors (reduce the risk of obesity associated with chronic treatment) and hERG channels (reduce the incidence of torsade des pointes) In animal models, the compund significantly inhibited apomorphine-induced climbing behavior, and Conditioned avoidance response (CAR) without catalepsy at the highest dose tested Compound had a higher threshold for catalepsy induction compared with that of the two currently marketed atypical antipsychotics, risperidone and clozapine.	18
 **265**	Cytotoxic towards human cancer cell lines (Ehrlich ascites carcinoma cells (EAC) in vitro)	IC_{50} (μM) = 0.12-0.13	All the tested compounds showed more toxicity than the 5-fluorouracil in vitro studies (IC_{50} = 0.38 μM)	19
Pyrane and benzopyrane				
 **266**	Anti-inflammatory (Carrageenin-induced hind-paw edema) Analgesic (Acetic acid writhing test)	% Inhibition = 23-62% % Protection = 22-60%	Week anti-inflammatory and analgesic activity The benzofuranyl ethers of coumarins were found to be most active amongst all the compounds. The Chloro and methoxy substitution in coumarin ring found to increase the activity	20
 **267**	Anti-HIV activity (tested against HIV-1 replication in acutely infected H9 lymphocytes)	EC_{50} = 1.88x10^{-4} μM Therapeutic index = 188,032	AZT EC_{50} = 0.045 μM Therapeutic index = 41,667	21

 **268**	Antioxidant (DPPH) Inhibition the soybean lipoxygenase Inhibition of trypsin Antiinflammatory (Carrageenin-induced hind-paw edema)	Reduction ability = 80.4% (0.5 mM, 60 min) Inhibition = 58.5–100% Inhibition of trypsin = 15–96.3% Inhibition = 48.7–58.9% (Indomethacin induced 57% protection at equivalent concentration)	The attempt to correlate the biological results with some physicochemical parameters was unsuccessful.	22
Piperazine				
 **269**	Acetylcholinesterase inhibitory activity	IC_{50} = 4.5 μM	Coumarins having phenylpiperazine substitution on the positions 3 and/or 4 with a suitable linking chain show significant anti-AChE activities. The inhibitory potency was strongly influenced by the length and shape of the spacer	23
 **270**	Cholinesterase inhibitory activity evaluated against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).	IC_{50} = 1.6-74 μM against AChE IC_{50} = 15-387 μM against BuChE	Highest AChE inhibitory activity with 26-fold selectivity for AChE respect to the BuChE. Mixed-mode inhibition pattern, in which both catalytic anionic subsite (CAS) and peripheral anionic binding site (PAS) are occupied by the ligand.	24
 **271**	Inhibitor of β-secretase (BACE-1*) in vitro*	IC_{50} = 0.093 μM	The best spacer is a methylene group The amide group linked to position 4 appears to be the most favourable In the *in vitro* enzymatic assay, the hydrophobicity of the derivatives appear to be a determinative parameter in the BACE-1 inhibitory activities.	25
 **272**	α_1-Adrenoceptor antagonists evaluated by induced contractions of rat anococcygeus smooth muscles according	pA_2 = 9.365* *The activity was expressed as pA_2=−log[compound]$_2$, in which [compound]$_2$ is defined as the measured concentrations of the compounds assayed according to Schild's methods.[26]	The most of compounds exhibited strong α1-AR antagonistic activity (pA_2 = 8.005-9.365) Better activity than prazosin. Structure–activity relationship: Small hydrophobic group at the terminal heterocyclic ring and ortho substituents on the phenyl ring of phenylpiperazine moiety were the essential structural factors for α1-AR antagonistic activity.	27
 **273**	Antiinflammatory (Carrageenin-induced hind-paw edema) Adjuvant-induced disease (AID) as model of rheumatoid arthritis	Inhibition % of induced Carrageenin Rat Paw Edema CPE % = 77.7% (Indomethacin, induced 47% protection at an equivalent concentration) Rats treated with	Hydrophilicity, the presence of a free 7-OH, and steric requirements for the substituent at position 8 are the most important factors in terms of SAR. Although the antiinflammatory mechanism explaining the activity on CPE remains unclear, the *in*	28

		compound did not develop severe arthritis	*vivo* antiinflammatory activity of the synthesized compounds seems to be related with their high HO· scavenging and reducing activity, in vitro.	
		Pyrimidine		
 274	Vasorelaxing activity effect on nor-epinephrine induced contracture in thoracic rat aortic rings	IC_{50} = 411 μM (IC_{50} prazocin 487 μM)	Increase in aqueous solubility while retaining good hydrophobic character of the overall molecule is the key for maintaining high relaxation activity.	29
		Other cycles		
 275	Inhibitors of the tumor-associated carbonic anhydrase isoforms IX and XII	K_{Is} (μM) = 0.0065-0.0686 (hCA IX) 0.0043-0.0598 (hCA XII)		30
 142	Inhibitors of amyloid-β aggregation	Plateau reduction (% inhibition) = 96	Ranging from a modest reduction of the equilibrium plateau to nearly complete inhibition Pronounced effect upon inhibition of Aβ aggregation when coumarin was functionalized with nitrogen containing ring structures benzothiazole and triazole Coumarin analogs exhibit a number of additional AD-associated pharmacological effects and thus possess the potential to serve as multi-target AD therapeutics	31
 276	Moderate triglyceride-lowering activity	Triglyceride lowering activity (%) = 45	3 mg/kg/day in the Swiss albino mouse model Several times better than fenofibrate [Triglyceride lowering activity = 36% (at 30 mg/kg)]	32
 253	Cytotoxic towards human cancer cell lines	Cell line / IC_{50} (μM) MCF-7 5.35 SK-N-MC 3.75 MDA-MB 231 10.32	The best compound is at least two-fold more potent than etoposide against MCF-7, SKN-MC, and MDA-MB 231 cell lines	33
 239	Antioxidant (DPPH) Antibacterial (*S. Epidermidis*, methicillin-resistant *S. aureus* (*MRSA*))	IC_{50} = 120 μM *S. epidermidis* MIC = 6.3 μM *MRSA* MIC = 25 μM		34

 277	In vitro antimalarial activity against CQ sensitive 3D7 strain of *P. falciparum.* In vivo antimalarial activity against multi-drug-resistant *P. yoelii nigeriensis* in mice at 96 mg/kg/day by oral route using Peters's procedure.	IC_{50} = 0.082–0.85 μM Suppression of 41.14% on day 4	Moderate activity Limitation: poor solubility both in oil and water	35
 278	*In vivo* anti-inflammatory effects by using the functional model of carrageen ininduced rat paw edema	% inhibition of induced carrageenin rat paw edema at 0.01 mmol/kg CPE % = 41-73%	Indomethacin induced 47% protection at an equivalent dose Lipophilicity does not increase in parallel to inhibition The in vivo anti-inflammatory activity seems to be related with their high HO· scavenging and reducing activities.	36

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