Indian Journal of Chemistry
Vol. 65, June 2026, pp. 615-623
DOI: 10.56042/ijc.v65i6.27689

Synthesis and properties of N-substituted amides and their isosteric analogs containing polycyclic fragments: I. N-((1S,2S,3S,5R)-(+)-isopinocampheyl) amides and thioamides

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Received 18 January 2026; accepted (revised) 15 June 2026

Preparation has been carried out of a focused library of N-((1S,2S,3S,5R)-(+)-isopinocampheyl)aryl amides and the matching thioamide derivatives, all with simple H, F, or Cl groups on the aryl part. The synthesis has turned out straightforward: enantiopure (1S,2S,3S,5R)-(+)-isopinocampheylamine has been coupled directly with the relevant aromatic acid chlorides or thioacyl chlorides. After work-up and purification, the products have been obtained in solid yields of 71–81%. Full confirmation has relied on melting point checks, full ^{1}H and ^{13}C NMR spectra, plus elemental analysis. SwissADME and SILICOS-IT predictions reveal low micromolar aqueous solubility (4.3–27.0 μM), which decrease markedly with aryl halogenation. Molinspiration LogP values range from 4.03 to 5.69, and of particular interest, C=O to C=S replacement further lowers solubility in matched pairs. PASSOnline screening highlights prostaglandin E_1 antagonism as the dominant predicted activity (Pa 0.763–0.838, Pi 0.001–0.002), alongside strong profiles for autoimmune disorders (Pa 0.630–0.759) and rheumatoid arthritis (Pa 0.559–0.739) treatment. The thioamide subset additionally shows anti-obesity potential (Pa 0.724–0.783). SwissTargetPrediction repeatedly suggests interactions with P2X purinoceptor 7, soluble epoxide hydrolase, acetylcholinesterase, muscarinic M_2 receptor, and histamine H_2 receptor.

Keywords: Isopinocampheylamine, N-Substituted amide, Thioamide, Computer screening, SwissADME, PASSOnline

The amide bond is still one of the most fundamental — and yeah, people keep calling it “privileged” — structural motifs in medicinal chemistry and related areas. We really like the α-ketoamide moiety in particular because of its versatility: it can form several directed hydrogen bonds simultaneously (donor and acceptor roles), and at the same time it fits nicely into precise interactions with biological targets[1]. That makes it a super useful building block for designing new ligands — honestly, it's hard to find another group that packs so much functionality into such a compact unit.

What makes it even better is that synthetic modifications are pretty straightforward — you can change substituents to tweak pharmacokinetic properties and improve binding to active sites without too much hassle[2]. For instance, adjusting the alkyl chains or adding polar groups nearby often helps balance solubility and metabolic stability while keeping (or even boosting) target affinity. In real life, this scaffold turns up in quite a few approved drugs and in a good number of promising bioactive compounds, backing up a fairly broad range of biological effects: antitumor and antiviral activities[3], anti-inflammatory and neurotropic properties[4–7], different ways to approach type 2 diabetes treatment[8], and selective inhibition of enzymes such as soluble epoxide hydrolase (sEH)[9,10]. Besides that, α-ketoamides have been quite commonly employed in the development of protease inhibitors. Among the earlier examples are telaprevir and boceprevir, both of which target the HCV NS3/4A protease. More recently, several groups have worked on peptidomimetic α-ketoamides directed at the SARS-CoV-2 main protease (Mpro), and some of these compounds demonstrated activity in cell-based experiments not only against coronaviruses but also against selected enteroviruses.

Targeted introduction of an amide fragment is still a very standard and reliable strategy in modern drug design, especially for anticancer targeted therapies. A classic example is bortezomib (Fig. 1, **1**), the first 26S proteasome inhibitor that made it to the clinic. Its peptidomimetic structure with the amide allows covalent interaction with the catalytic threonine in the proteasome active site — that's basically what drives its efficacy in multiple myeloma and mantle cell lymphoma[11]. The way the boronic acid warhead

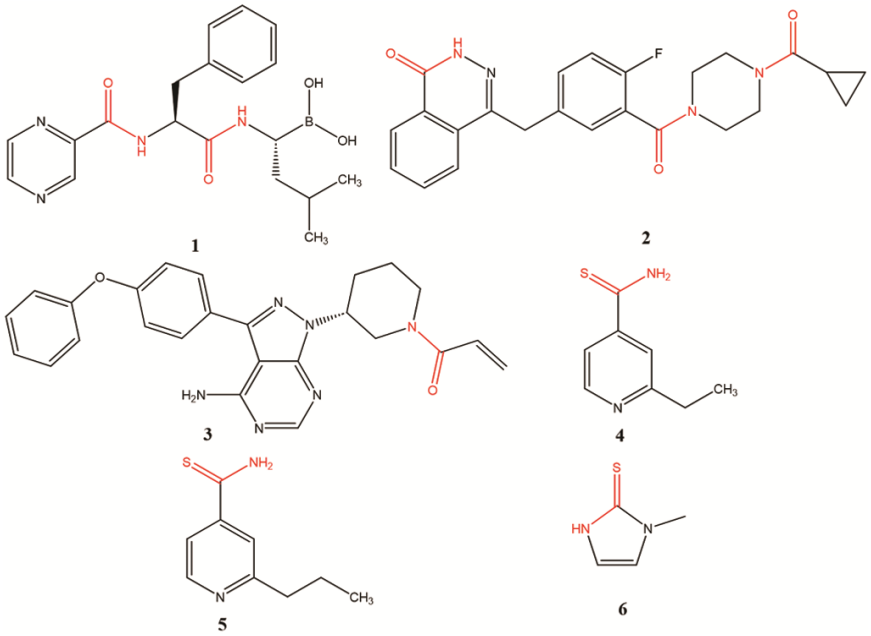


Fig. 1 — Known drugs containing an amide or thioamide group

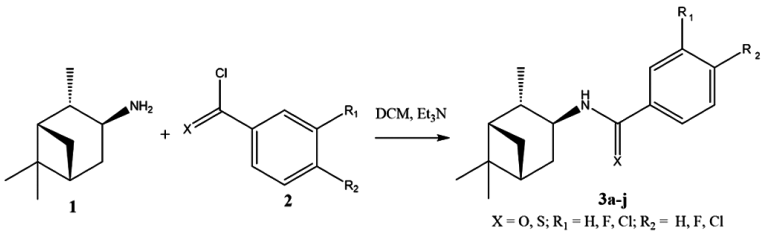
works together with the amide backbone to trap the enzyme irreversibly is pretty elegant when you look at the crystal structures.

Olaparib (Fig. 1, **2**) is another well-known amide-containing drug. As a PARP inhibitor, it blocks the NAD^+-dependent catalytic site and works particularly well in tumors with defective homologous recombination repair, like those with BRCA1/2 mutations[12,13]. It's become a go-to in ovarian, breast, and prostate cancers with those genetic backgrounds — the synthetic lethality concept here is one of the nicer success stories in precision oncology.

And then there's ibrutinib (Fig. 1, **3**), a covalent BTK inhibitor used a lot in B-cell lymphomas. Its structural features (that acrylamide electrophile) let it engage the target efficiently and keep suppressing BTK signaling for a long time[14]. The prolonged off-rate from the cysteine residue means you get durable inhibition even with once-daily dosing, which has really changed the treatment landscape for CLL and some lymphomas.

Alongside regular amides, thioamide derivatives are also quite interesting in practice. Replacing the carbonyl oxygen with sulfur (C=O → C=S) changes polarity and the donor–acceptor properties, which can shift binding patterns to targets in useful ways — sometimes improving selectivity, sometimes helping with penetration or stability against certain enzymes. Ethionamide (Fig. 1, **4**) is a good example — it's a second-line antitubercular prodrug. Inside mycobacteria, after oxidative bioactivation (mainly by the EthA flavin monooxygenase), it forms NAD adducts that inhibit enoyl-ACP reductase InhA and block mycolic acid biosynthesis in the cell wall[14]. Its close analog prothionamide (Fig. 1, **5**) works basically the same way and is often used against drug-resistant TB, especially in regimens for MDR-TB where you need to layer in second-line agents[16]. One thing to note is that these thioamides can sometimes cause hypothyroidism as a side effect (similar mechanism to antithyroid drugs), which clinicians have to monitor.

Thioamides show up outside antimicrobials too: methimazole (thiamazole) (Fig. 1, **6**) is still a key antithyroid drug. It primarily works by inhibiting thyroid peroxidase, which blocks the iodination and coupling reactions essential for producing T3 and T4 (Ref. 17). Carbimazole is frequently used as an alternative (it gets metabolized to methimazole in the body). Propylthiouracil (PTU) is another drug from the same thionamide group, though it differs in some respects — it is occasionally selected over methimazole during the first trimester of pregnancy owing to reports of a somewhat lower risk of certain birth defects, even though PTU has its own concern regarding a higher potential for serious liver toxicity. Both carry the rare but serious risk of agranulocytosis, so monitoring blood counts is standard practice whichever one is prescribed. Despite these limitations, thionamides of this type have remained primary treatments for hyperthyroidism for many



Scheme 1 — Preparation of N-substituted amides and thioamides bearing an isopinocampheyl fragment

Table 1 — Yields and properties of compounds **3a-j**

Compd	X	R_1	R_2	m.p. (°C)	LogP	Solubility (μM)	Yield (%)
3a	O	H	H	145-146	4.03	27.0	76
3b	O	H	F	156-157	4.19	14.4	75
3c	O	F	H	160-161	4.17	14.4	73
3d	O	H	Cl	113-114	4.71	6.7	81
3e	O	Cl	H	108-109	4.68	6.7	74
3f	S	H	H	80-81	5.01	17.1	78
3g	S	H	F	86-87	5.17	9.1	71
3h	S	F	H	82-83	5.15	9.1	74
3i	S	H	Cl	77-78	5.69	4.3	73
3j	S	Cl	H	75-76	5.66	4.3	78

decades — they are effective in most patients and physicians have extensive experience with their use.

Taken together, these examples show that amides and thioamides are really robust, clinically proven pharmacophores. That gives strong support for continuing rational design of new derivatives — whether tweaking for better ADME, exploring covalent inhibition strategies, or targeting emerging pathogens and resistant cancers — and using computer-assisted profiling (docking, MD simulations, QSAR) to predict which modifications are most likely to pay off. The field keeps evolving, and these motifs aren't going anywhere soon.

Results and Discussion

We prepared a series of N-substituted amides and thioamides bearing an isopinocampheyl fragment. The target compounds – N-((1S,2S,3S,5R)-(+)-isopinocampheyl)amides and their thioamide analogs – were synthesized through direct acylation of enantiopure (1S,2S,3S,5R)-(+)-isopino camphey lamine with the corresponding aromatic acid chlorides or thioacyl chlorides in dichloromethane (DCM), as shown in Scheme 1.

The calculated water solubility of compounds **3a-j** was determined using the SwissADME online service (http://www.swissadme.ch/). The SILICOS-IT method was used for the calculation. The lipophilicity coefficient (LogP) was calculated using the Molinspiration online service (https://molinspiration.com). The obtained experimental and calculated data are presented in Table 1. Data for thioanalogues is provided for comparison.

Looking at the data in Table 1, we observed that the melting points of the amides **3a–e** fall in the range of 108–161°C. Notably, the chlorinated derivatives (**3d** and **3e**) melt at lower temperatures compared to their hydrogen- or fluorine-substituted counterparts. The corresponding thioamides **3f–j** exhibit even lower melting points overall, spanning 75–87°C. Interestingly, the substituent effect persists in the thioamide series: chlorine-substituted analogs again show reduced melting points relative to the H- and F-substituted ones.

The calculated lipophilicity coefficient of compounds **3a–j** is in the range from 4.03 to 5.69, while the lipophilicity coefficient of thioamides is approximately 1.0 higher than that of the corresponding amides.

From the SwissADME and SILICOS-IT predictions, it's clear that sticking a halogen on the aromatic ring brings down water solubility quite reliably — and the effect shows up in both amide and thioamide compounds. For the amides **3a–e**, we could see fluorine cutting the value roughly in half (27.0 μM for the plain **3a** drops to 14.4 μM with F in **3b** and

Table 2 — Effect of the chalcogen atom on the ^{1}H and ^{13}C chemical shifts in the NMR spectra of compounds **3c** and **3h**

Chalcogen atom X	Bond	
	H-N	C=X
O	6.83	167.71
S	8.03	198.47

3c), while chlorine hits harder, reducing it about four times over to 6.7 μM in the chloro versions **3d** and **3e**. This was quite consistent with the thioamides **3f–j**: fluorine again halved things (17.1 μM in **3f** to 9.1 μM in **3g**/**3h**), and chlorine gave a similar fourfold drop to 4.3 μM in **3i**/**3j**.

What's more, when we compare matched pairs, changing the amide to thioamide (C=O to C=S) pushes solubility lower still, across the board — examples include 27.0 μM (**3a**) *vs* 17.1 μM (**3f**), 14.4 μM (**3b**/**3c**) *vs* 9.1 μM (**3g**/**3h**), and 6.7 μM (**3d**/**3e**) *vs* 4.3 μM (**3i**/**3j**). The reason the *meta* and *para* isomers always match (**3b**/**3c**, **3d**/**3e**, **3g**/**3h**, **3i**/**3j**) is simple: the SILICOS-IT method treats them the same way.

In the ^{1}H NMR spectra of compounds **3a–e**, the signal of the amide -N*H* proton is observed in the region of 6.83–7.07 ppm and is presented in the form of a doublet with a spin-spin interaction constant of about 8 Hz. Thioamides **3f–j** are characterized by a downfield shift of this signal to 7.74–8.03 ppm; for an example, see Table 2. From the general patterns for amides and thioamides, one can distinguish the signals of the protons of the framework isopinocamphenyl fragment in the region of 0.92–3.71 ppm and the signals of the aromatic ring protons in the region of 7.11–7.94 ppm.

The ^{13}C NMR spectra of compounds **3a–e** contains signals from carbon atoms corresponding to the isopinocamphenyl fragment in the range 16.26–51.36 ppm. Signals from the aromatic ring carbon atoms are present in the range 114.62–159.26 ppm, with the signal for the fluorine-substituted carbon atom appearing as a doublet with $^{1}J_{C\text{-}F}$ at approximately 240 Hz. Signals from the C(=O) group are present in the range 165.30–167.87 ppm.

The ^{13}C NMR spectra of compounds **3f–j** contains signals from carbon atoms corresponding to the isopinocamphenyl fragment in the range 16.27–56.06 ppm. Signals from the carbon atoms of the aromatic ring are present in the range 113.47–164.32 ppm, with the signal for the carbon atom substituted by a fluorine atom appearing as a doublet with $^{1}J_{C\text{-}F}$ at approximately 240 Hz. Signals from the C(=S) group are present at 198.47–199.77 ppm.

A computer screening of possible biological activities and a search for the most likely biological targets for compounds **3a-j** were conducted. Activity calculations were performed using the PASSOnline online service (https://www.way2drug.com/-PASSOnline/methods.php), and the most likely biological targets were assessed using the SwissTargetPrediction online service (http://www.swisstargetprediction.ch).

As can be seen from Table 3, for all compounds **3a-j** Prostaglandin E1 antagonist activity is predicted as the most probable one (Pa = 0.763-0.838 with low Pi values = 0.001-0.002). In addition, the whole series shows consistently high probabilities for "Autoimmune disorders treatment" (Pa = 0.630-0.759; Pi = 0.005-0.010) and "Rheumatoid arthritis treatment" (Pa = 0.559-0.739; Pi = 0.004-0.007), with oxygen analogs **3a-e** generally demonstrating higher Pa values than the corresponding thioamides **3f-j**. For thioamides **3f-j**, "Antiobesity" is additionally predicted with relatively high confidence (Pa = 0.724-0.783; Pi = 0.005), while other secondary effects (*e.g.*, phobic disorders treatment, antidyskinetic or antineurotic activities) appear for individual representatives. According to SwissTargetPrediction, the most frequently suggested targets within the series are P2X purinoceptor 7, epoxide hydratase, acetylcholinesterase, muscarinic acetylcholine receptor M2 and histamine H2 receptor, which points to a potential involvement of inflammation- and neurotransmission-related pathways.

Experimental Section

All of chemicals used in the current study were purchased from commercial vendors (Sigma Aldrich) and employed as received without further purification. All solvents were purified and dried using standard methods prior to use. Nuclear magnetic resonance (^{1}H, ^{13}C) spectra were recorded on a Bruker Avance 600 (USA) spectrometer with chemical shifts reported as ppm at 600, 150 MHz, respectively in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard. Elemental analysis was performed using a Perkin Elmer 2400 Series II analyzer (USA). The melting points were measured on an OptiMelt MPA100 melting point apparatus (Stanford Research Systems, USA).

General procedure for the synthesis of N-((1S,2S,3S,5R)-(+)-Isopinocampheyl)amides and -thioamides, 3a-j

To a solution of 1.00 mmol corresponding aromatic acid chloride **2a-e** or thioacyl chlorides **2f-j** in 10 mL

Table 3 — Activity screening and assessment of probable activity of compounds **3a-j** against some biotargets.

Compd	Probability of activity (Pa)	Probability of inactivity (Pi)	Activity	Target
3a	0,838	0,001	Prostaglandin E1 antagonist	Acetylcholinesterase
	0,759	0,005	Autoimmune disorders treatment	P2X purinoceptor 7
	0,753	0,049	Ubiquinol-cytochrome-c reductase inhibitor	Epoxide hydratase
	0,743	0,057	Phobic disorders treatment	Muscarinic acetylcholine receptor M2
	0,739	0,004	Rheumatoid arthritis treatment	N-acylsphingosine-amidohydrolase
	0,652	0,071	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	
3b	0,791	0,002	Prostaglandin E1 antagonist	Epoxide hydratase
	0,758	0,005	Autoimmune disorders treatment	Acetylcholinesterase
	0,735	0,004	Rheumatoid arthritis treatment	Somatostatin receptor 3
	0,710	0,015	Antidyskinetic	P2X purinoceptor 7
	0,675	0,048	Antineurotic	11-beta-hydroxysteroid dehydrogenase 1
	0,594	0,126	Phobic disorders treatment	Steroid 5-alpha-reductase 1
3c	0,772	0,002	Prostaglandin E1 antagonist	Epoxide hydratase
	0,753	0,005	Autoimmune disorders treatment	Metabotropic glutamate receptor 5
	0,732	0,004	Rheumatoid arthritis treatment	Acetylcholinesterase
	0,670	0,022	Antidyskinetic	P2X purinoceptor 7
	0,634	0,062	Nootropic	Dopamine transporter
	0,618	0,065	Antineurotic	Norepinephrine transporter
3d	0,819	0,002	Prostaglandin E1 antagonist	P2X purinoceptor 7
	0,834	0,022	Phobic disorders treatment	Epoxide hydratase
	0,728	0,005	Autoimmune disorders treatment	Acetylcholinesterase
	0,709	0,004	Rheumatoid arthritis treatment	Sigma opioid receptor
	0,746	0,052	Ubiquinol-cytochrome-c reductase inhibitor	11-beta-hydroxysteroid dehydrogenase 1
	0,655	0,025	Antidyskinetic	Muscarinic acetylcholine receptor M2
3e	0,813	0,002	Prostaglandin E1 antagonist	P2X purinoceptor 7
	0,806	0,031	Phobic disorders treatment	11-beta-hydroxysteroid dehydrogenase 1
	0,709	0,006	Autoimmune disorders treatment	Metabotropic glutamate receptor 5
	0,685	0,005	Rheumatoid arthritis treatment	Muscarinic acetylcholine receptor M2
	0,675	0,021	Antidyskinetic	Muscarinic acetylcholine receptor M3
	0,694	0,071	Ubiquinol-cytochrome-c reductase inhibitor	Epoxide hydratase
3f	0,832	0,002	Prostaglandin E1 antagonist	Histamine H2 receptor
	0,749	0,005	Antiobesity	Kappa Opioid receptor
	0,692	0,007	Autoimmune disorders treatment	Muscarinic acetylcholine receptor M4
	0,688	0,004	Albendazole monooxygenase inhibitor	Muscarinic acetylcholine receptor M5
	0,620	0,005	Rheumatoid arthritis treatment	Dopamine transporter
	0,536	0,003	ATP-binding cassette A1 stimulant	Sigma opioid receptor
3g	0,784	0,002	Prostaglandin E1 antagonist	Dopamine D3 receptor
	0,737	0,005	Antiobesity	Histamine H2 receptor
	0,699	0,006	Autoimmune disorders treatment	Sigma opioid receptor *(by homology)*
	0,627	0,005	Rheumatoid arthritis treatment	Beta amyloid A4 protein
	0,583	0,077	Antineurotic	Troponin, cardiac muscle
	0,488	0,019	Albendazole monooxygenase inhibitor	Progesterone receptor
3h	0,763	0,002	Prostaglandin E1 antagonist	Histamine H2 receptor
	0,724	0,005	Antiobesity	Sigma opioid receptor *(by homology)*
	0,695	0,007	Autoimmune disorders treatment	Dopamine D3 receptor
	0,629	0,005	Rheumatoid arthritis treatment	Dopamine transporter
				Muscarinic acetylcholine receptor M2
	0,455	0,004	ATP-binding cassette A1 stimulant	Muscarinic acetylcholine receptor M4
	0,470	0,022	Albendazole monooxygenase inhibitor	

(*Contd.*)

Table 3 — Activity screening and assessment of probable activity of compounds **3a-j** against some biotargets (*Contd*.).

Compd	Probability of activity (Pa)	Probability of inactivity (Pi)	Activity	Target
3i	0,812	0,002	Prostaglandin E1 antagonist	P2X purinoceptor 7
	0,783	0,005	Antiobesity	C-X-C chemokine receptor type 3
	0,657	0,009	Autoimmune disorders treatment	Quinone reductase 2
	0,683	0,084	Phobic disorders treatment	Histamine H2 receptor
	0,586	0,006	Rheumatoid arthritis treatment	Serotonin transporter
	0,572	0,056	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor	11-beta-hydroxysteroid dehydrogenase 2
3j	0,807	0,002	Prostaglandin E1 antagonist	P2X purinoceptor 7
	0,769	0,005	Antiobesity	C-X-C chemokine receptor type 3
	0,630	0,010	Autoimmune disorders treatment	Fatty acid desaturase 1
	0,559	0,007	Rheumatoid arthritis treatment	Monoglyceride lipase *(by homology)*
	0,628	0,110	Phobic disorders treatment	Cyclooxygenase-2
	0,578	0,080	Antineurotic	Beta amyloid A4 protein

of dichloromethane were added 1.05 mmol of (1S,2S,3S,5R)-(+)-isopinocampheylamine **1** and 2.10 mmol of Et_3N at 25°C. The reaction mass was stirred at RT for 16 hours. The reaction mixture was then evaporated under reduced pressure; the residue was purified by silica gel chromatography with PE/EA (8/1) as eluent. The structure of the obtained compounds was confirmed using ^1H and ^{13}C NMR spectroscopy and elemental analysis.

N-((1S,2S,3S,5R)-(+)-Isopinocampheyl)benzamide, 3a

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), benzoyl chloride (140 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). White solid. Yield 195 mg (76%). m.p.145-146°C. ^1H NMR (DMSO-d_6): δ 0.93 – 1.01 (m, 9H, CH_3), 1.43 – 2.17 (m, 7H, Isop.), 3.52 – 3.57 (m, 1H, C*H*-NH), 6.84 (d, CH-N*H*, J = 8.4 Hz, 1H), 7.38 – 7.47 (m, 2H, arom), 7.48 – 7.57 (m, 3H, arom), 8.27 (s, 1H, N*H*-Ph); ^{13}C NMR (DMSO-d_6): δ 16.27 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.42 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 39.84 (s, 1C, Isop.), 40.36 (s, 1C, Isop.), 45.83 (s, 1C, Isop.), 51.36 (s, 1C, *C*H-NH), 127.46 (s, 2C, arom), 128.80 (s, 1C, arom), 132.07 (s, 2C, arom), 135.11 (s, 1C, *C*-CO), 167.87 (s, 1C, *C*=O). Anal. %: ($C_{17}H_{23}NO$) C 79.27, H 9.04, N 5.39. Calcd., %: C 79.33, H 9.01, N 5.44. M = 257.18

4-Fluoro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzamide, 3b

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), 4-fluorobenzoyl chloride (159 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). White solid. Yield 206 mg (75%). m.p.156-157°C. ^1H NMR (DMSO-d_6): δ 0.92 – 0.97 (m, 6H, CH_3), 0.98 – 1.01 (m, 3H, CH_3), 1.42 – 1.52 (m, 1H, Isop.), 1.53 – 1.63 (m, 2H, Isop.), 1.74 – 1.80 (m, 2H, Isop.), 1.82 – 1.91 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.), 3.51 – 3.56 (m, 1H, C*H*-NH), 7.07 (d, CH-N*H*, J = 8.3 Hz, 1H), 7.32 – 7.38 (m, 2H, arom), 7.88 – 7.94 (m, 2H, arom); ^{13}C NMR (DMSO-d_6): δ 16.27 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.34 (s, 1C, Isop.), 40.66 (s, 1C, Isop.), 46.23 (s, 1C, Isop.), 51.16 (s, 1C, *C*H-NH), 115.83 (s, 2C, arom), 130.01 (s, 2C, arom), 131.45 (s, 1C, *C*-CO), 159.26 (d, 1C, J = 239.1 Hz, C-F), 165.30 (s, 1C, *C*=O). Anal. %: ($C_{17}H_{22}FNO$) C 74.17, H 8.04, N 5.13. Calcd., %: C 74.15, H 8.05, N 5.09. M = 275.37

3-Fluoro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzamide, 3c

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol 3-fluorobenzoyl chloride (159 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). White solid. Yield 201 mg (73%). m.p.160-161°C. ^1H NMR (DMSO-d_6): δ 0.92 – 0.96 (m, 6H, CH_3), 0.98 – 1.02 (m, 3H, CH_3), 1.42 – 1.52 (m, 1H, Isop.), 1.53 – 1.63 (m, 2H, Isop.), 1.74 – 1.80 (m, 2H, Isop.), 1.82 – 1.91 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.), 3.51 – 3.56 (m, 1H, C*H*-NH), 6.83 (d, CH-N*H*, J = 8.3 Hz, 1H), 7.33 – 7.41 (m, 1H, arom), 7.46 – 7.55 (m, 1H, arom), 7.65 – 7.74 (m, 2H, arom); ^{13}C NMR (DMSO-d_6): δ 16.26 (s, 1C, CH_3), 25.32 (s, 2C, CH_3), 29.71 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.34 (s, 1C, Isop.), 40.63 (s, 1C,

Isop.), 46.26 (s, 1C, Isop.), 51.16 (s, 1C, *C*H-NH), 114.62 (s, 1C, arom), 114.77 (s, 1C, arom), 118.87 (s, 1C, arom), 123.22 (s, 1C, arom), 135.87 (s, 1C, *C*-CO), 159.09 (d, 1C, J = 239.1 Hz, C-F), 167.71 (s, 1C, *C*=O). Anal. %: ($C_{17}H_{22}FNO$) C 74.13, H 8.08, N 5.12. Calcd., %: C 74.15, H 8.05, N 5.09. M = 275.37

4-Chloro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzamide, 3d

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), 4-chlorobenzoyl chloride (175 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). White solid. Yield 236 mg (81%). m.p.113-114°C. ^{1}H NMR (DMSO-d_6): δ 0.92 – 1.02 (m, 9H, CH_3), 1.47 – 1.63 (m, 3H, Isop.), 1.74 – 1.87 (m, 2H, Isop.), 1.88 – 1.94 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.), 3.51 – 3.56 (m, 1H, C*H*-NH), 6.84 (d, CH-N*H*, J = 8.2 Hz, 1H), 7.44 – 7.52 (m, 2H, arom), 7.76 – 7.82 (m, 2H, arom); ^{13}C NMR (DMSO-d_6): δ 16.26 (s, 1C, CH_3), 25.32 (s, 2C, CH_3), 29.41 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.34 (s, 1C, Isop.), 40.66 (s, 1C, Isop.), 46.23 (s, 1C, Isop.), 51.16 (s, 1C, *C*H-NH), 128.71 (s, 2C, arom), 129.13 (s, 1C, C-Cl), 133.65 (s, 2C, arom), 136.94 (s, 1C, *C*-CO), 167.21 (s, 1C, *C*=O). Anal. %: ($C_{17}H_{22}ClNO$) C 66.96, H 7.62, N 4.73. Calcd., %: C 66.97, H 7.60, N 4.80. M = 291.82

3-Chloro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzamide, 3e

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), 3-chlorobenzoyl chloride (175 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). White solid. Yield 216 mg (74%). m.p.108-109°C. ^{1}H NMR (DMSO-d_6): δ 0.92 –1.02 (m, 9H, CH_3), 1.42 – 1.66 (m, 3H, Isop.), 1.74 – 1.85 (m, 2H, Isop.), 1.86 – 1.91 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.), 3.51 – 3.56 (m, 1H, C*H*-NH), 6.89 (d, CH-N*H*, J = 8.3 Hz, 1H), 7.46 – 7.54 (m, 1H, arom), 7.59 – 7.65 (m, 1H, arom), 7.77 – 7.83 (m, 1H, arom); ^{13}C NMR (DMSO-d_6): δ 16.26 (s, 1C, CH_3), 25.32 (s, 2C, CH_3), 29.71 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.34 (s, 1C, Isop.), 40.63 (s, 1C, Isop.), 46.23 (s, 1C, Isop.), 51.16 (s, 1C, *C*H-NH), 125.66 (s, 1C, arom), 128.81 (s, 1C, arom), 130.39 (s, 1C, arom), 130.71 (s, 1C, arom), 134.35 (s, 1C, C-Cl), 135.31 (s, 1C, *C*-CO), 167.13 (s, 1C, *C*=O). Anal. %: ($C_{17}H_{22}ClNO$) C 66.98, H 7.58, N 4.82. Calcd., %: C 66.97, H 7.60, N 4.80. M = 291.82

N-((1S,2S,3S,5R)-(+)-Isopinocampheyl)benzothioa mide, 3f

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), benzothioyl chloride (157 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). Light yellow solid. Yield 213 mg (78%). m.p.80-81°C. ^{1}H NMR (DMSO-d_6): δ 0.93 – 1.02 (m, 9H, CH_3), 1.42 – 2.17 (m, 7H, Isop.), 3.64 – 3.71 (m, 1H, C*H*-NH), 7.39 – 7.45 (m, 1H, arom), 7.56 – 7.63 (m, 1H, arom), 7.81 (d, CH-N*H*, J = 7.5 Hz, 1H), 7.88 – 7.95 (m, 2H, arom),. ^{13}C NMR (DMSO-d_6): δ 16.54 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.14 (s, 1C, Isop.), 40.76 (s, 1C, Isop.), 46.33 (s, 1C, Isop.), 55.96 (s, 1C, *C*H-NH), 127.02 (s, 1C, arom), 128.75 (s, 2C, arom), 130.22 (s, 2C, arom), 142.46 (s, 1C, *C*-CS), 199.77 (s, 1C, *C*=S). Anal. %: ($C_{17}H_{23}NS$) C 74.71, H 8.51, N 5.09. Calcd., %: C 74.67, H 8.48, N 5.12. M = 273.44

4-Fluoro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzothioamide, 3g

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), 4-fluorobenzothioyl chloride (175 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). Light yellow solid. Yield 207 mg (71%). m.p.86-87°C. ^{1}H NMR (DMSO-d_6): δ 0.92 – 1.01 (m, 9H, CH_3), 1.42– 1.65 (m, 3H, Isop.), 1.74 – 1.99 (m, 3H, Isop.), 2.08 – 2.17 (m, 1H, Isop.) 3.63 – 3.71 (m, 1H, C*H*-NH), 7.19 – 7.18 (m, 2H, arom), 7.61 – 7.69 (m, 2H, arom), 8.01 (d, CH-N*H*, J = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 16.57 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 39.94 (s, 1C, Isop.), 40.76 (s, 1C, Isop.), 46.33 (s, 1C, Isop.), 55.96 (s, 1C, *C*H-NH), 115.95 (s, 2C, arom), 129.16 (s, 2C, arom), 139.82 (s, 1C, *C*-CS), 163.32 (d, 1C, J = 240.1 Hz, *C*-F), 199.21 (s, 1C, *C*=S). Anal. %: ($C_{17}H_{22}FNS$) C 70.04, H 7.66, N 4.82. Calcd., %: C 70.06, H 7.61, N 4.81. M = 291.43

3-Fluoro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzothioamide, 3h

Prepared from (1S,2S,3S,5R)-(+)-isopinocamph eylamine (160 mg, 1.05 mmol), 3-fluorobenzothioyl chloride (175 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). Light yellow solid. Yield 216 mg (74%). m.p.82-83°C. ^{1}H NMR (DMSO-d_6): δ 0.92 –1.01 (m, 9H, CH_3), 1.42 – 1.69 (m, 3H, Isop.), 1.74 – 1.99 (m, 3H, Isop.), 2.08 – 2.17 (m, 1H, Isop.)

3.63 – 3.71 (m, 1H, C*H*-NH), 7.11 – 7.25 (m, 1H, arom), 7.47 – 7.57 (m, 2H, arom) 7.77 – 7.82 (m, 1H, arom) 8.03 (d, CH-N*H*, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 16.27 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.64 (s, 1C, Isop.), 40.16 (s, 1C, Isop.), 40.77 (s, 1C, Isop.), 46.33 (s, 1C, Isop.), 56.06 (s, 1C, *C*H-NH), 113.47 (s, 1C, arom), 118.74 (s, 1C, arom), 122.66 (s, 1C, arom), 130.35 (s, 1C, arom), 144.05 (s, 1C, *C*-CS), 164.32 (d, 1C, J = 240.1 Hz, *C*-F), 198.47 (s, 1C, *C*=S). Anal. %: ($C_{17}H_{22}$FNS) C 70.11, H 7.58, N 4.79. Calcd., %: C 70.06, H 7.61, N 4.81. M = 291.43

4-Chloro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzothioamide, 3i

Prepared from (1S,2S,3S,5R)-(+)-isopinocam pheylamine (160 mg, 1.05 mmol), 4-chlorobenzothioyl chloride (191 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). Light yellow solid. Yield 225 mg (73%). m.p.77-78°C. ^{1}H NMR (DMSO-d_6): δ 0.92 – 1.01 (m, 9H, CH_3), 1.42 – 1.63 (m, 2H, Isop.), 1.64 – 1.70 (m, 1H, Isop.), 1.76 – 1.91 (m, 2H, Isop.), 1.90 – 1.99 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.) 3.63 – 3.71 (m, 1H, C*H*-NH), 7.45 – 7.51 (m, 2H, arom), 7.61 – 7.67 (m, 2H, arom), 7.74 (d, CH-N*H*, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 16.27 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.14 (s, 1C, Isop.), 40.76 (s, 1C, Isop.), 46.33 (s, 1C, Isop.), 55.96 (s, 1C, *C*H-NH), 128.03 (s, 2C, arom), 129.24 (s, 1C, *C*-Cl), 135.45 (s, 2C, arom), 141.95 (s, 1C, *C*-CS), 199.11 (s, 1C, *C*=S). Anal. %: ($C_{17}H_{22}$ClNS) C 66.35, H 7.18, N 4.52. Calcd., %: C 66.32, H 7.20, N 4.55. M = 307.88, 127.96, 129.24, 135.34, 141.96, 198.83.

3-Chloro-N-((1S,2S,3S,5R)-(+)-isopinocampheyl) benzothioamide, 3j

Prepared from (1S,2S,3S,5R)-(+)-isopinocampheylamine (160 mg, 1.05 mmol), 3-chlorobenzothioyl chloride (191 mg, 1.00 mmol) and Et_3N (212 mg, 2.10 mmol). Light yellow solid. Yield 240 mg (78%). m.p.75-76°C. ^{1}H NMR (DMSO-d_6): δ 0.92 – 1.01 (m, 9H, CH_3), 1.42 – 1.63 (m, 2H, Isop.), 1.64 – 1.70 (m, 1H, Isop.), 1.76 – 1.91 (m, 2H, Isop.), 1.90 – 1.99 (m, 1H, Isop.), 2.08 – 2.17 (m, 1H, Isop.) 3.63 – 3.71 (m, 1H, C*H*-NH), 7.35 – 7.41 (m, 1H, arom), 7.45 – 7.51 (m, 1H, arom), 7.73 – 7.77 (m, 1H, arom), 7.83 – 7.89 (m, 1H, arom), 7.94 (d, CH-N*H*, *J* = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 16.57 (s, 1C, CH_3), 25.33 (s, 2C, CH_3), 29.72 (s, 1C, Isop.), 31.91 (s, 1C, Isop.), 38.62 (s, 1C, Isop.), 40.14 (s, 1C, Isop.), 40.76 (s, 1C, Isop.), 46.33 (s, 1C, Isop.), 55.96 (s, 1C, *C*H-NH), 125.33 (s, 1C, arom), 127.27 (s, 1C, arom), 129.84 (s, 1C, arom), 131.85 (s, 1C, arom), 135.55 (s, 1C, *C*-Cl), 143.57 (s, 1C, *C*-CS), 198.99 (s, 1C, *C*=S). Anal. %: ($C_{17}H_{22}$ClNS) C 66.31, H 7.22, N 4.56. Calcd., %: C 66.32, H 7.20, N 4.55. M = 307.88

Conclusion

N-((1S,2S,3S,5R)-(+)-isopinocampheyl)aryl amides and thioamides were conveniently prepared from the corresponding acyl and thioacyl chlorides under mild conditions and characterized by melting points, ^{1}H/^{13}C NMR and elemental analysis. *In silico* profiling (SwissADME, SILICOS-IT) indicates low micromolar aqueous solubility (4.3-27.0 μM) that decreases upon aryl halogenation and upon the C=O to C=S isosteric replacement, while Molinspiration LogP values remain high (4.03-5.69). PASSOnline screening identifies Prostaglandin E1 antagonist as the dominant predicted activity across the series (Pa = 0.763-0.838; Pi = 0.001-0.002), alongside autoimmune disorders and rheumatoid arthritis treatment profiles, and antiobesity potential for thioamides. The recurrent predicted targets (P2X purinoceptor 7, epoxide hydratase, acetylcholinesterase, muscarinic acetylcholine receptor M2 and histamine H2 receptor) support further experimental evaluation of this polycyclic (thio) amide scaffold.

Acknowledgement

The authors express their sincere gratitude to the Department of Chemistry at NMAMIT, Nitte, for providing the necessary laboratory facilities to conduct this research. Special thanks are extended to the Sophisticated Analytical Instrument Facility at CSIR-Central Drug Research Institute (CDRI), Lucknow; Manipal Institute of Technology (MIT), MAHE; and the University of Mysore for their assistance with spectral analysis. Finally, the authors acknowledge the support provided by the Petroleum Engineering Department, College of Engineering, University of Kerbala, Iraq.

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