One-pot Multicomponent Synthesis and Antimicrobial Evaluation of Novel Tricyclic Indenopyrimidine-2-amines

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ABSTRACT

The synthesis of novel tricyclic indenopyrimidine-2-amines from 3,3-dimethyl-/3-methyl-2*H*-indanones has achieved by base-catalysed one-pot three-component reaction. The desired products are formed within 10 hours after addition at reflux temperature. This multicomponent approach offers a viable protocol for the construction of indenopyrimidine-2-amines in single-step without the isolation of the intermediates 3,3-dimethyl/3-methyl-2-(4-substituted benzylidene)-2,3-dihydro-1*H*-inden-1-ones. All the synthesized compounds have been screened for antimicrobial activity and some of the derivatives show comparable activity against bacterial and fungal isolates.

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INTRODUCTION

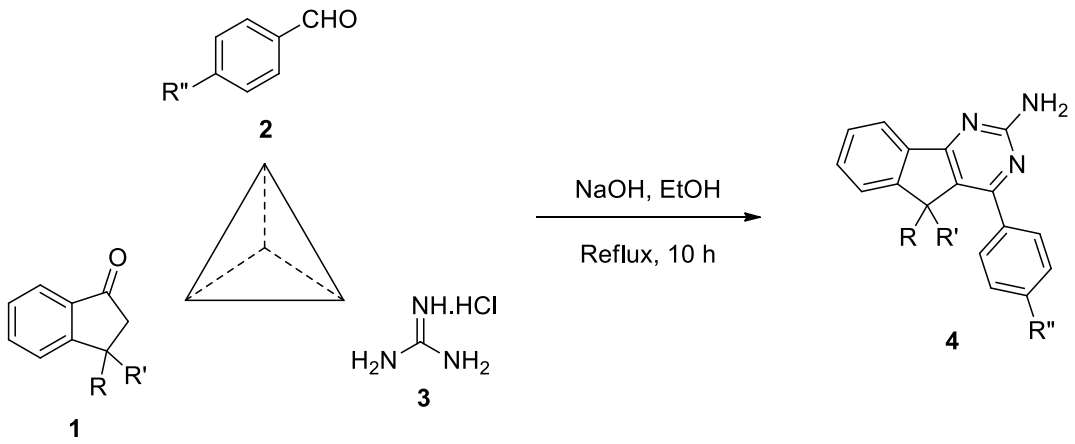
Nitrogen containing heterocyclic compounds constitutes the largest and vital family of organic compounds due to their enormous synthetic and biological utility. Pyrimidine, a heterocyclic six membered ring containing two nitrogen atoms possesses a vital place in the pharmaceutical and medicinal fields due to its antifungal, anti-inflammatory, antipyretic, anti-depressant and anticancer activities.[1] The fused pyrimidines such as indenopyrimidines have been extensively studied by various groups of scientists because of their chemical and biological importance. The indenopyrimidines were found to possess various biologically activities such as antibacterial,[2-4] antiallergic,[3,5] antitumor,[3,4,6,7] antifolate,[8] tyrosine kinase,[9] calcium channel antagonists,[10] antiinflammatory, analgesic,[11] antihypertensive,[12] antileishmanial,[13] tuberculostatic,[14] anticonvulsants,[15] and antiaggressive activities. [16]

The condensation of *CCC* bis-electrophiles and *NCN* bis-nucleophiles is the most classical [3+3] approach to the pyrimidines synthesis using diverse catalytic system. [17] The use of NaOH, NaOMe, ionic liquids and metal complexes or metal oxides such as silver loaded ZnO_2 to the pyrimidine synthesis have been well described in the literature.[18] On the other hand, the multicomponent reactions are the vital protocols for synthesis of organic compounds due to advantages such as high atom efficiency, high chemical yields, lesser reaction time, lesser waste and minimum by-product formation which makes it superior to the classical protocols.[18] The indenopyrimidines syntheses through multicomponent reactions have been extensively studied by several research groups.[18-20]

Owing the biological applications of pyrimidines and fused pyrimidines, the preparation of indenopyrimidines and their functionalized derivatives is of notable interest to reveal novel derivatives and explore new applications. These indenopyrimidine derivatives can offer strong opportunity to the organic as well as the medicinal chemists to develop more useful drugs. In continuation of our work in the synthesis of various heterocyclic compounds [21-29] and owing the importance of indenopyrimidine amines as the most privileged building blocks in organic and medicinal chemistry we reported here one-pot three-component synthesis of novel tricyclic indenopyrimidine derivatives and evaluate their antimicrobial activities.

RESULTS AND DISCUSSION

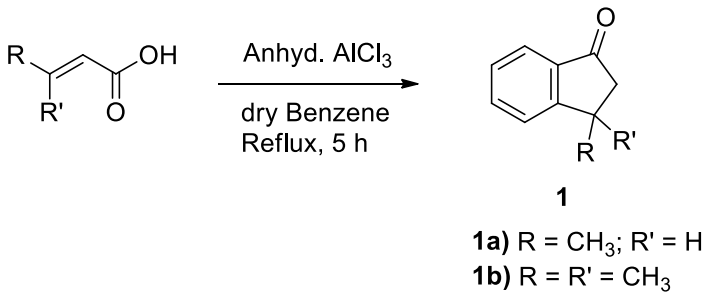
The literature revealed that 2-benzylideneindan-1-one undergoes dimerization upon heating in guanidine carbonate using DMF as a solvent. This was possible due to the abstraction of one of the methylene protons of 5-membered ring of indene system to give a cross-conjugate enolate followed by intermolecular Michael addition on a second molecule.[30,31] In another report, the treatment of 2-benzylideneindan-1-one with guanidine-HCl using solid NaOH in refluxing ethanol afforded indenopyrimidine in excellent yield.[32] Therefore, we thought worthwhile to investigate the multicomponent strategy for the preparation of 2-aminopyrimidine fused with five-membered ring of the indene system (Method **A**) (Scheme 1).



4a) R = CH_3; R' = R" = H, **4b)** R' = H; R = R" = CH_3, **4c)** R = CH_3; R' = H, R" = Cl, **4d)** R = CH_3; R' = H, R" = OCH_3, **4e)** R = CH_3; R' = H, R" = F, **4f)** R = R' = CH_3; R" = H, **4g)** R = R' = R" = CH_3, **4h)** R = R' = CH_3; R" = Cl, **4i)** R = R' = CH_3; R" = OCH_3, **4j)** R = R' = CH_3; R" = F

Scheme 1. One-pot three-component synthesis of indenopyrimidine-2-amines **4a-j**

The Friedel-Craft reaction of 3-substituted but-2-enoic acid in refluxing dry benzene using anhydrous $AlCl_3$ afforded the corresponding 3,3-disubstituted-2*H*-indanones (Scheme 2).[33]



Scheme 2. Synthesis of 3,3-disubstituted-2*H*-indanone **1a-b**

Having 3,3-disubstituted-2*H*-indanone in hand, the optimization study for a one-pot three-component reaction involving 3-methyl-2*H*-indanone (1.0 equiv.), benzaldehyde (1.0 equiv.) and guanidinium hydrochloride (2.0 equiv.) was carried out by performing a series of experiments using various reaction conditions. The results are summarized in Table **1**. When the reaction was performed in the absence of base and solvent then no product formation was observed at room temperature or heating at 120 °C for 24 h (Table **1**, entries 1 and 2). The reaction was attempted using various bases such as TEA, pyridine, K_2CO_3, Cs_2CO_3, KOH and NaOH. The most encouraging results were obtained in KOH and NaOH (Table **1**, entries 7 and 8, respectively). By increasing the quantity of NaOH from 2 to 5 equivalents in refluxing ethanol afforded the indenopyrimidine product **4a** in 73% yield (Table **1**, entry 10).

Table 1. Optimization of reaction condition

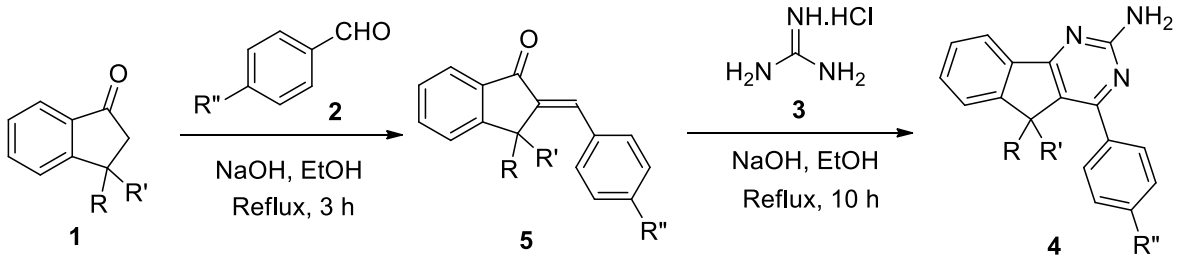
Entry	Base	Solvent	Temp °C	Time h	Yield[a] %
1	-	-	rt	24	NR
2	-	-	120	24	NR
3	TEA (3.0 eq)	EtOH	Reflux	10	8
4	Pyridine (3.0 eq)	EtOH	Reflux	10	11
5	K_2CO_3 (3.0 eq)	EtOH	Reflux	10	15
6	Cs_2CO_3 (3.0 eq)	EtOH	Reflux	10	17
7	KOH (2.0 eq)	EtOH	Reflux	10	39
8	NaOH (2.0 eq)	EtOH	Reflux	10	45
9	NaOH (3.0 eq)	EtOH	Reflux	10	59
10	NaOH (5.0 eq)	EtOH	Reflux	10	73
11	NaOH (5.0 eq)	EtOH	Reflux	12	71
12	NaOH (6.0 eq)	EtOH	Reflux	10	67
13	NaOH (5.0 eq)	MeOH	Reflux	10	61
14	NaOH (5.0 eq)	DMF	90	10	53

15	NaOH (5.0 eq)	MeCN	Reflux	10	51

Reaction conditions: 3-Methyl-2*H*-indanone (1.0 equiv.), benzaldehyde (1.0 equiv.) and guanidinium hydrochloride (2.0 equiv.), Base, Solvent (10 V), temperature.
[a]Yields of isolated products.

Repeating the experiment for 12 h resulted in a significant decrease of yield (71%, Table **1**, entry 11). Whereas the reaction in other solvents such as MeOH, DMF and acetonitrile gave the desired product **4a** in 61%, 53% and 51% yield, respectively (Table **1**, entries 13-15). The best condition for one-pot three-component reaction appeared thus to be the use of 5.0 equivalent of NaOH in refluxing ethanol (Table **1**, entry 10) and consequently, used for further exploration of the preparing compound **4**, having a number of substituents. The results are summarized in Table **2**. To our delight all the substituted indenopyrimidine-2-amines resulted into good yields (66-83%) and were not particularly substituents dependent.

In order to compare the effect of multicomponent strategy on the reaction yield, it was considered worthwhile to attempt the synthesis of **4** in stepwise manner (Method **B**) (Scheme **3**).



4a) R = CH_3; R' = R" = H, **4b)** R' = H; R = R" = CH_3, **4c)** R = CH_3; R' = H, R" = Cl, **4d)** R = CH_3; R' = H, R" = OCH_3, **4e)** R = CH_3; R' = H, R" = F, **4f)** R = R' = CH_3; R" = H, **4g)** R = R' = R" = CH_3, **4h)** R = R' = CH_3; R" = Cl, **4i)** R = R' = CH_3; R" = OCH_3, **4j)** R = R' = CH_3; R" = F

Scheme 3. Synthesis of indenopyrimidine-2-amine **4a-j** in stepwise manner

Thus, 3-methyl-2*H*-indanone **1a** was converted to 2-benzylidene-3-methyl-2,3-dihydro-1*H*-inden-1-one **5a** which was refluxed with guanidinium hydrochloride in ethanol using NaOH as base catalyst afforded indenopyrimidine-2-amine **4a** in 65% yield as compared to 73% yield obtained in one-pot multicomponent strategy. Other derivatives **4b-j** were synthesized in a similar manner in 49-71% yield (Table **2**).

Table 2. Yields of a series of indenopyrimidine derivatives **3a-j**

Entry	R	R′	R″	Product	% Yield	
					Method A[a]	Method B[b]
1	CH_3	H	H	**4a**	73	65

2	CH_3	H	CH_3	**4b**	76	63
3	CH_3	H	Cl	**4c**	70	59
4	CH_3	H	OMe	**4d**	68	53
5	CH_3	H	F	**4e**	83	71
6	CH_3	CH_3	H	**4f**	79	61
7	CH_3	CH_3	CH_3	**4g**	66	49
8	CH_3	CH_3	Cl	**4h**	74	58
9	CH_3	CH_3	OMe	**4i**	78	67
10	CH_3	CH_3	F	**4j**	81	69

[a]Yields of isolated products **4** with respect to **1**
[b]Yields of isolated products **4** with respect to **5**

The IR spectrum of compound **4a** revealed three medium intensity bands at 3301, 3150 cm^{-1} and 1485 cm^{-1} which corresponds to –NH and –C=N stretching, respectively. The 400 MHz ^{1}H NMR spectrum of **4a** was quite informative. It displayed a three-proton doublet (J= 7.2 Hz) at δ 1.05 which can undoubtedly be ascribed to methyl group at C_5. A one-proton quartet (J= 7.2 Hz) appeared at 4.53 ascribed to C5-H of the 5-membered ring of indene system. The two-proton singlet appeared at δ 6.69 belongs to $–NH_2$ group. In the aromatic region one-proton doublet located at δ 7.67 (J = 7.2 Hz) which can be ascribed to aromatic ring. The other eight protons of the aromatic rings appeared as one three-proton and the other five-proton multiplets in the region δ 7.94-7.85 & 7.57-7.45, respectively. In case of ^{13}C NMR spectral analysis of **4a**, the methyl carbon of 5-membered ring of indene and amino carbon resonated at 19.2 ppm and 159.6 ppm, respectively. The other signals of magnetically non-equivalent carbon atoms appeared at their respective chemical shifts. The mass spectral analysis of **4a** has shown the molecular ion peak at m/z 288 $[M+H]^+$.

The structures of all novel synthesized products **4a-j** were determined by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and MS) methods (Supporting Information File-1) and purity was further determined by its elemental analysis.

Antimicrobial Activities

The Minimum inhibitory concentrations (MICs) of all compounds **4a-j** were evaluated against Gram-positive (*Bacillus cereus* MTCC1272 and *Staphylococcus aureus* MTCC737) and Gram-negative (*Escherichia coli* MTCC118 and *Yersinia enterocolitica* MTCC861) bacteria, and the fungal species *Candida albicans* MTCC227 by the broth macrodilution method[34] using standard drugs ampicillin and miconazole. As shown in Table **3,** the compounds **4e** and **4j**

(containing *p-fluoro* substituents) exhibited comparable activity to the reference standard ampicillin against the Gram (-ve) bacterial strain *E. coli* evidenced by minimum inhibitory concentration of 78.1 µg/ml. While compounds **4b** (containing *p-methyl* substituents), **4e** (containing *p-fluoro* substituents), **4f** and **4j** exhibited MIC of 39.06 µg/ml against the Gram (-ve) bacterial strain *Y. enterocolitica*. The MIC value of these compounds was found comparable to the reference standard ampicillin. The compounds **4a, 4c, 4d, 4e, 4f** and **4g** were having MIC of 78.01 µg/ml against the Gram (+ve) bacterial strains *S. aureus.* The compound **4j** was found an excellent compound to be active against all Gram (-ve) and Gram (+ve) bacterial strains *E. coli, Y. enterocolitica,* and *S. aureus*. Regarding the antifungal evaluation, the compounds **4c**, **4d, 4e, 4f, 4i** and **4j** showed comparable antifungal activity against *C. albicans* with MIC 78.1 µg/ml as compared to reference standard miconazole. All other compounds displayed lower activity against all bacterial and fungal isolates.

Table 3. Minimum inhibitory concentrations (MICs) of test compounds **4** against fungal and bacterial isolates.

Test compounds	**MIC (µg/mL)**				
	Gram-negative bacteria		**Gram-positive bacteria**		**Fungi**
	Escherichia coli	*Yersinia enterocolitica*	*Bacillus cereus*	*Staphylococcus aureus*	*Candida albicans*
4a	156.25	78.1	78.1	78.1	156.25
4b	156.25	39.06	78.1	156.25	156.25
4c	156.25	78.1	78.1	78.1	78.1
4d	156.25	78.1	78.1	78.1	78.1
4e	78.1	39.06	78.1	78.1	78.1
4f	156.25	39.06	78.1	78.1	78.1
4g	156.25	78.1	78.1	78.1	156.25
4h	156.25	156.25	78.1	156.25	156.25
4i	156.25	156.25	78.1	156.25	78.1
4j	78.1	39.06	39.06	156.25	78.1
Ampicillin[#]	78.1	39.06	39.06	78.1	-
Miconazole[##]	-	-	-	-	78.1

[#]Standard antibacterial agent. [##]Standard antifungal agent.

But there is still a need to carry out further modifications in indenopyrimidines structure in order to detect more efficacious antimicrobial lead molecules. Moreover, cytotoxicity evaluation on test microorganisms and mammalian cell lines is also necessary to establish

correlation between antimicrobial potential and therapeutic safety of the indenopyrimidines under investigation. Follow-up studies with most promising and non-cytotoxic derivatives are important to elucidate their possible molecular mechanism of action.

CONCLUSIONS

In summary, a one-pot multicomponent synthesis of novel tricyclic indenopyrimidine-2-amines from 3,3-disubstituted-2*H*-indanone has been reported. This multicomponent approach offers a viable protocol for the construction of indenopyrimidine-2-amines in single-step without the isolation of the intermediates 3,3-dimethyl/3-methyl-2-(4-substituted benzylidene)-2,3-dihydro-1*H*-inden-1-one. All the synthesized compounds have been screened for antimicrobial activity and some of the derivatives show comparable activity against bacterial and fungal isolates. Notably, tricyclic indenopyrimidine-2-amines can be further used as versatile building blocks for the synthesis of various useful derivatives that may be of great interest in developing the novel pyrazole-based drugs. The investigation about further derivatization of indenopyrimidine-2-amines is still ongoing in our laboratory.

MATERIALS AND METHODS

Melting points were determined in open glass capillaries on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature on FT-NMR Cryo-magnet Spectrometer 400 MHz (Bruker) in DMSO-d_6/$CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard (δ = 0 ppm), and the values were reported in the following order: chemical shift (δ = 0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J* in Hz), and integration. IR spectra were taken as KBr pellets on a Perkin Elmer RXI FT-IR spectrometer. The mass spectra were recorded on a JOEL JMS 600 mass spectrometer at an ionising potential of 70eV (EI) electron impact ionisation mode using the direct inlet system. All the reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel 60 F254 (mesh); spots were visualised under UV light at 254 nm. Elemental analyses were obtained using a Carlo Erba EA1108 microanalyser.

Synthesis of 3,3-dimethyl-/3-methyl-2*H*-indanone 1a-b[33]

A solution of crotonic acid (25 g, 29.07 mmol) in benzene (75 mL) was added dropwise in suspension of $AlCl_3$ (115.95 g, 87.21 mmol) in dry benzene (112 mL). The mixture was refluxed for 5 hours. The reaction progress was monitored by thin layer chromatography at regular time intervals. After completion of reaction, the mixture was poured into ice cooled 10% HCl and extracted with diethyl ether. The organic layer was washed with aqueous saturated solution of $NaHCO_3$ and water. Then the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 34.2 g of 3-methyl-2*H*-indanone **1a**.

Oil, 81% yield; TLC solvent system: 10% EtOAc: pet-ether, R_f: 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.61 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.51 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H, Ar*H*), 7.37 (t, *J* = 6.4 Hz, 1H, Ar*H*), 3.47-3.42 (m, 1H, CH_3CH-), 2.95 (dd, *J* = 19.2 Hz, 7.6 Hz, 1H, -COCH_2), 2.29 (dd, *J* = 19.2 Hz, 3.6 Hz, 1H, -COCH_2), 1.41 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 147 $[M+H]^+$. *Anal*. Calcd for $C_{20}H_{19}N_3O$: C, 82.16; H, 6.89%. Found: C, 82.09; H, 6.93%.

The 3,3-dimethyl-2*H*-indanone **1b** is also prepared from 3-methyl crotonic acid by following the same procedure as for **1a**.

3,3-Dimethyl-2*H*-indanone 1b

Oil, yield 89%; TLC solvent system: 10% EtOAc: pet-ether, R_f: 0.6; ^{1}H NMR ($CDCl_3$, 400 mHz): δ 7.71 (d, *J*= 8.0 Hz, 1H, ArH), 7.71-7.35 (m, 3H, Ar*H*), 2.59 (s, 2H, CH_2CO), 1.43 (s, 6H, 2 x CH_3). ESI-MS (m/z): 161 $[M+H]^+$. *Anal*. Calcd for $C_{20}H_{19}N_3O$: C, 82.46; H, 7.55%. Found: C, 82.39; H, 7.51%.

Method A

Synthesis of 4-(4-substituted phenyl)-5-methyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amines 4

An equimolar mixture of aldehydes (1 mmol) and 3,3-disubstituted-2*H*-indanones (1 mmol) was dissolved in ethanol (10 mL) at room temperature, followed by the addition of solid NaOH (5 mmol) and guanidinium hydrochloride (2 mmol) and refluxed for 10 hours. The reaction progress was monitored by thin layer chromatography at regular time intervals. When the reaction was complete, ethanol was removed under high vacuum. The crude compound was

purified by column chromatography using 100-200 mesh silica. The solvent was evaporated and dried under high vacuum to afford compounds **4a-j**.

5-Methyl-4-phenyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4a

Off-white solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.5; m.p. 140-143 °C. IR (υ cm^{-1}, KBr): 3301, 3150 (NH str), 1485 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94-7.88 (m, 3H, Ar*H*), 7.67 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.57-7.46 (m, 5H, Ar*H*), 6.69 (bs, 2H, NH_2), 4.53 (q, *J* = 7.2 Hz, 1H, CH_3C*H*-), 1.05 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C=N), 163.2 (C=N), 159.7, 138.8, 135.5, 132.2, 128.7, 127.9, 126.6, 125.3, 124.2, 122.6, 121.7, 119.1, 36.5, 19.1 (CH_3). ESI-MS (m/z): 274.26 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37%. Found: C, 78.95; H, 5.47; N, 15.31%.

5-Methyl-4-(4-methylphenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4b

Off-white solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.6; m.p. 210-211 °C. IR (υ cm^{-1}, KBr): 3295, 3165 (NH str), 1489 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.85 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.67 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.55 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.34 (d, *J* = 7.6 Hz, 2H, Ar*H*), 6.65 (s, 2H, NH_2), 4.52 (q, *J* = 7.2 Hz, 1H, CH_3C*H*-), 2.40 (s, 3H, ArCH_3), 1.07 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C=N), 163.4 (C=N), 159.9, 138.6, 135.4, 130.9, 129.7, 128.3, 126.1, 125.3, 125.2, 122.3, 121.5, 119.6, 35.3, 19.1 (CH_3), 18.9 (CH_3). ESI-MS (m/z): 288.28 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62%. Found: C, 79.35; H, 5.89; N, 14.66%.

4-(4-Chlorophenyl)-5-methyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4c

Off-white solid, TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.6; m.p. 191-194 °C. IR (υ cm^{-1}, KBr): 3308, 3205 (NH str), 1491 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.88 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.67 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.62-7.54 (m, 3H, Ar*H*), 7.48 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.73 (s, 2H, NH_2), 4.53 (q, *J* = 7.2 Hz, 1H, CH_3C*H*-), 1.08 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=N), 162.3 (C=N), 159.7, 139.1, 135.1, 133.9, 130.7, 128.3, 127.9, 126.1, 125.2, 122.3, 121.5, 119.6, 35.3, 19.1

(CH_3). ESI-MS (m/z): 308.17 [M+H; $^{35}Cl]^+$, 310.19 [M+H, $^{37}Cl]^+$. *Anal*. Calcd for $C_{18}H_{14}ClN_3$: C, 70.24; H, 4.58; N, 13.65%. Found: C, 70.16; H, 4.54; N, 13.69%.

4-(4-Methoxyphenyl)-5-methyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4d

Off-white solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.3; m.p. 192-195 °C. IR (υ cm^{-1}, KBr): 3316, 3175 (NH str), 1490 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.88 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.67 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.55 (t, 7.2 Hz, 1H, Ar*H*), 7.47 (t, 7.2 Hz, 1H, Ar*H*), 7.08 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.62 (s, 2H, NH_2), 4.52 (q, *J* = 7.2 Hz, 1H, CH_3C*H*-), 3.85 (s, 3H, OCH_3), 1.10 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C=N), 163.1 (C=N), 159.9, 159.3 (C-O), 138.6, 135.4, 128.3, 126.1, 125.3, 125.1, 122.3, 121.5, 119.1, 112.3, 48.3 (OCH_3), 37.3, 19.2 (CH_3). ESI-MS (m/z): 304.24 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85%. Found: C, 75.15; H, 5.60; N, 13.91%.

4-(4-Fluorophenyl)-5-methyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4e

Light yellow solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.4; m.p. 216-218 °C. IR (υ cm^{-1}, KBr): 3310, 3185 (NH str), 1487 (C=N str). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.90-7.86 (m, 2H, Ar*H*), 7.54-7.44 (m, 3H, Ar*H*), 7.22 (t, *J* = 7.6 Hz, 2H, Ar*H*), 5.17 (s, 2H, NH_2), 4.35 (q, *J* = 7.2 Hz, 1H, CH_3C*H*-), 1.16 (d, *J*= 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C=N), 162.3 (C=N), 161.5 (C-F), 159.4, 139.5, 135.7, 130.1, 128.3, 126.1, 125.2, 122.3, 121.5, 119.6, 115.1, 35.3, 19.1 (CH_3). ESI-MS (m/z): 292.24 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{14}FN_3$: C, 74.21; H, 4.84; N, 14.42%. Found: C, 74.15; H, 4.79; N, 14.37%.

5,5-Dimethyl-4-phenyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4f

Yellow solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.5; m.p. 145-147 °C. IR (υ cm^{-1}, KBr): 3326, 3155 (NH str), 1487 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, *J* = 7.6 Hz, 1H, ArH), 7.59-7.38 (m, 8H, ArH), 6.69 (s, 2H, NH_2), 1.22 (s, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C=N), 163.2 (C=N), 159.1, 151.8, 133.5, 132.1, 128.9, 127.9, 126.6, 125.3, 122.6, 122.1, 121.7, 119.1, 41.1, 25.3 (2 x CH_3). ESI-MS (m/z): 288.28 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62%. Found: C, 79.35; H, 5.91; N, 14.67%.

5,5-Dimethyl-4-(4-methylphenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4g

Brown solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.6; m.p. 215-217 °C. IR (υ cm^{-1}, KBr): 3336, 3167 (NH str), 1491 (C=N str). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.84 (d, *J* = 7.2 Hz, 1H, ArH), 7.58-7.23 (m, 7H, ArH), 6.66 (s, 2H, NH_2), 2.39 (s, 3H, CH_3), 1.23 (s, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=N), 163.1 (C=N), 159.1, 151.2, 132.4, 130.9, 129.7, 128.3, 126.1, 125.3, 125.1, 122.3, 121.5, 119.6, 41.3, 28.1 (2 x CH_3), 19.2 (CH_3). ESI-MS (m/z): 302.29 $[M+H]^+$. *Anal*. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94%. Found: C, 79.59; H, 6.31; N, 13.99%.

4-(4-Chlorophenyl)-5,5-dimethyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4h

Brown solid, TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.6; m.p. 195-197 °C. IR (υ cm^{-1}, KBr): 3396, 3208 (NH str), 1495 (C=N str). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.4 Hz, 1H, ArH), 7.53-7.37 (m, 5H, ArH), 7.36 (d, J = 8.8 Hz, 2H, ArH), 5.12, (s, 2H, NH_2), 1.30 (s, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=N), 162.3 (C=N), 159.7, 151.1, 134.1, 133.9, 130.7, 128.3, 127.9, 126.1, 122.3, 122.1, 121.5, 119.6, 41.3, 28.1 (2 x CH_3). ESI-MS (m/z): 322.26 $[M+H; {}^{35}Cl]^+$, 324.27 $[M+H, {}^{37}Cl]^+$. *Anal*. Calcd for $C_{19}H_{16}ClN_3$: C, 70.91; H, 5.01; N, 13.06%. Found: C, 70.86; H, 4.95; N, 13.01%.

4-(4-Methoxyphenyl)-5,5-dimethyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4i

Yellow solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.3; m.p. 202-204 °C. IR (υ cm^{-1}, KBr): 3316, 3185 (NH str), 1488 (C=N str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (d, *J* = 7.2 Hz, 1H, ArH), 7.58 (d, *J* = 7.6 Hz, 1H, ArH), 7.52 (dt, *J* = 7.2, 1.2 Hz, 1H, ArH), 7.42 (dt, *J* = 7.2, 1.2 Hz, 1H, ArH), 7.35 (d, *J* = 8.8 Hz, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H, ArH), 6.65 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3), 1.24 (s, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=N), 163.1 (C=N), 159.6, 159.1 (C-O), 151.6, 133.4, 127.3, 125.9, 125.3, 122.3, 121.9, 121.5, 119.1, 112.3, 49.3 (OCH_3), 41.3, 28.2 (2 x CH_3). ESI-MS (m/z): 318.35 $[M+H]^+$. *Anal*. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24%. Found: C, 75.60; H, 5.97; N, 13.30%.

4-(4-Fluorophenyl)-5,5-dimethyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine 4j

Yellow solid, TLC solvent system: 50% EtOAc in pet-ether, R_f: 0.4; m.p. 212-214 °C. IR (υ cm^{-1}, KBr): 3329, 3197 (NH str), 1497 (C=N str). ^{1}H NMR ($CDCl_3$, 400 mHz): δ 7.98 (d, 1H, *J*= 7.2 Hz, ArH), 7.51-7.05 (m, 7H, NH_2, ArH), 5.35 (s, 2H, NH_2), 1.43 (s, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2 (C=N), 162.1 (C=N), 161.7 (C-F), 159.4, 151.5, 133.7, 130.1, 128.3, 126.1, 122.9, 122.3, 121.5, 119.1, 115.2, 41.3, 28.1 (2 x CH_3). ESI-MS (m/z): 306.29 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{16}FN_3$: C, 74.74; H, 5.28; N, 13.76%. Found: C, 74.69; H, 5.22; N, 13.71%.

Method B

Synthesis of 3-methyl-2-(4-substituted benzylidene)-2,3-dihydro-1*H*-inden-1-one 5

Aromatic aldehyde (1.0 equivalent) was added to a solution of 3-methylindanone (1.0 equivalent) in 10 V of EtOH followed by dropwise addition of an aqueous solution of NaOH (3.0 equivalents). The solution was refluxed for 2 hours. The reaction progress was monitored by thin layer chromatography at regular time intervals. After completion of reaction, the mixture was extracted with EtOAc and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Then, recrystallized with EtOH and dried under reduced pressure to get pure product **5a-j**.

2-Benzylidene-3-methyl-2,3-dihydro-1*H*-inden-1-one 5a[35]

Brown solid, 76% yield; TLC solvent system: 10% EtOAc in pet-ether, R_f: 0.6; m.p. 78-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.68-7.63 (m, 4H, Ar*H*), 7.56 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H, Ar*H*), 7.48-7.40 (m, 4H, =CH, Ar*H*), 4.44 (q, *J* = 6.8 Hz, 1H, CH_3CH-), 1.42 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 235 $[M+H]^+$.

3-Methyl-2-(4-methylbenzylidene)-2,3-dihydro-1*H*-inden-1-one 5b

Off-white solid, 69% yield; TLC solvent system: 10% EtOAc in pet-ether, R_f: 0.8; m.p. 75- 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.66-7.62 (m, 2H, Ar*H*), 7.57-7.54 (m, 3H, =CH, Ar*H*), 7.43 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.27 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.41 (q, *J* = 6.8 Hz, 1H, CH_3CH-), 2.41 (s, 3H, $ArCH_3$), 1.42 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 249 $[M+H]^+$.

2-(4-Chlorobenzylidene)-3-methyl-2,3-dihydro-1*H*-inden-1-one 5c

Light brown solid, 72% yield; TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.8; m.p. 84-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.66 (dt, *J* = 7.6 & 1.2Hz, 1H, Ar*H*), 7.61-7.55 (m, 4H, Ar*H*), 7.46-7.42 (m, 3H, =CH, Ar*H*), 4.39 (q, *J* = 6.8 Hz, 1H, CH_3CH-), 1.40 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 269 [M+H; ^{35}Cl]$^+$, 271 [M+H, ^{37}Cl]$^+$.

2-(4-Methoxybenzylidene)-3-methyl-2,3-dihydro-1*H*-inden-1-one 5d

Brown solid, 82% yield; TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.7; m.p. 69-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.65-7.61 (m, 4H, =CH, Ar*H*), 7.55 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.98 (d, *J* = 8.8 Hz, 2H, Ar*H*), 4.37 (q, *J* = 6.8 Hz, 1H, CH_3CH-), 3.87 (s, 3H, OCH_3), 1.43 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 265 [M+H]$^+$.

2-(4-Fluorobenzylidene)-3-methyl-2,3-dihydro-1H-inden-1-one 5e

Yellow solid, 83% yield; TLC solvent system: 20% EtOAc in pet-ether, R_f: 0.5; m.p. 75-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.67-7.63 (m, 4H, =CH, Ar*H*), 7.56 (dd, *J* = 7.6 & 0.8 Hz, 1H, Ar*H*), 7.44 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.15 (t, *J* = 8.8 Hz, 2H, Ar*H*), 4.39 (q, *J* = 6.8 Hz, 1H, CH_3CH-), 1.41 (d, *J* = 6.8 Hz, 3H, CH_3). ESI-MS (m/z): 253 [M+H]$^+$.

2-Benzylidene-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one 5f

Oil, 80% yield, TLC solvent system: 10% EtOAc in pet-ether, R_f: 0.6; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 8.00 (d, *J* = 6.8 Hz, 1H, ArH), 7.87 (d, *J* = 7.6 Hz, 1H, ArH), 7.78 (s, 1H, =CH), 7.66-7.63 (m, 3H, ArH), 7.61 (d, *J* = 1.2 Hz, 4H, ArH), 1.52 (s, 6H, 2 x CH_3). ESI-MS (m/z): 248 [M+H]$^+$.

3,3-Dimethyl-2-(4-methylbenzylidene)-2,3-dihydro-1*H*-inden-1-one 5g

Oil, 77% yield; TLC solvent system: 10% EtOAc in pet-ether, R_f: 0.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.66-7.27 (m, 8H, =CH, Ar*H*), 2.41 (s, 3H, $ArCH_3$), 1.52 (s, 6H, 2 x CH_3). ESI-MS (m/z): 263 [M+H]$^+$.

2-(4-Chlorobenzylidene)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one 5h

Oil, 96% yield, TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.8; ^{1}H-NMR($CDCl_3$, 400 Hz) δ 8.00 (d, *J* = 8.8 Hz, 2H, ArH), 7.86 (d, *J* = 8.0 Hz, 1H, ArH), 7.78 (d, *J* = 8.0 Hz, 1H, ArH), 7.70-7.61 (m, 3H, =CH, ArH), 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 1.51 (s, 6H, 2 x CH_3). ESI-MS (m/z): 283 [M+H; ^{35}Cl]$^+$, 285 [M+H, ^{37}Cl]$^+$.

2-(4-Methoxybenzylidene)-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one 5i

Oil, 80% yield; TLC solvent system: 30% EtOAc in pet-ether, R_f: 0.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.65-7.61 (m, 4H, =CH, Ar*H*), 7.55 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.98 (d, *J* = 8.8 Hz, 2H, Ar*H*), 3.87 (s, 3H, OCH_3), 1.51 (s, 6H, 2 x CH_3). ESI-MS (m/z): 279 [M+H]$^+$.

2-(4-Fluorobenzylidene)-3,3-dimethyl-2,3-dihydro-1H-inden-1-one 5j

Oil, 84% yield; TLC solvent system: 20% EtOAc in pet-ether, R_f: 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.67-7.44 (m, 8H, =CH, Ar*H*), 1.51 (s, 6H, 2 x CH_3). ESI-MS (m/z): 267 [M+H]$^+$.

Synthesis of 5H-indeno[1,2-*d*]pyrimidin-2-amines 4

Solid NaOH (5.0 eq.) was added to a solution containing 2.0 eq. of guanidine-HCl in 10 mL of EtOH and stirred for an hour. The mixture was filtered to remove salt. The filtrate was added into a solution of corresponding sample of compound **5** (1.0 eq.) in another 10 mL of ethanol and reflux for 10 h. The reaction was monitored by thin layer chromatography. After completion of the reaction, ethanol was removed under high vacuum. The crude compound was purified by column chromatography. The solvent was evaporated and dried under high vacuum to afford compound **4a-j**. The isolated yield for each compound is given in Table-**2**.

Biological Assay

Test Microorganisms

Bacterial cultures (*Bacillus cereus* MTCC1272, *Staphylococcus aureus* MTCC737, *Escherichia coli* MTCC118, *Yersinia enterocolitica* MTCC861) and fungus *Candida albicans* MTCC227 were obtained from Microbial Type Culture Collection, IMTECH, Chandigarh

(India). Cultures were regularly maintained in the laboratory using standard media and incubation conditions.

Antimicrobial Activity

Indenopyrimidine-2-amines **4** were evaluated for their antimicrobial activities by broth macrodilution method as described previously by Sood et al.[34] Briefly, to prepare the stock solution, 10 mg of the test compounds were dissolved in DMSO (4 mL) and similarly, the standard drugs ampicillin and miconazole were dissolved in appropriate quantity of sterile distilled water (2.5 mg/mL). The bacterial and fungal inocula were made in saline solution (0.85% NaCl) and cell counts were adjusted to 5 x 10^7cfu/mL by using 0.5 McFarland standard. MICs of test compounds and test drugs were determined in sterile test tubes containing 2.0 mL of nutrient broth or Mueller-Hinton broth (for bacteria) and Sabouraud dextrose broth (for *Candida*). Two mL stock solution of test compounds and standard antimicrobial agents were added to first tube of their respective series and diluted serially to obtain different concentrations. The resultant diluted concentrations of test compounds and standard antimicrobial agents were 2500, 1250, 625, 312.5, 156.25, 78.1, 39.06, 19.53, 9.76 μg/mL. Broth tubes were inoculated with 10 μL of microbial suspension so that final counts were 5 x 10^5cfu/mL. Tubes containing medium or medium plus DMSO, and tubes without microbial inoculum served as growth and sterility controls, respectively. Broth tubes were incubated at 35-37 °C for 24 h and examined for the presence or absence of growth. The minimum concentration of test compounds and standard antimicrobials that resulted in complete growth inhibition was recorded as MIC.

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SUPPORTING INFORMATION

The supporting information is available in the file “Supporting Information File-1”

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