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A SOLVENT–FREE, ONE-POT ACCESS TO SOME QUINOLINE– AND PYRAZOL– ANNULATED HETEROCYCLES AND THEIR BIOLOGICAL EVALUATION

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ABSTRACT

A one-pot synthesis of some quinoline and pyrazol annulated heterocycles has been achieved via domino/Knoevenagel-hetero-Diels-Alder reaction, by combining 2-methyl-2-(4-methylpent-3-en-1-yl)-2H-thiopyrano[2,3-b]quinoline-3-carbaldehyde and O-alkenylated acetophenone as typical aldehyde and ketone based substrates, respectively, each with 5-pyrazolone under solvent-free environment. The reaction underwent smoothly, generating oxabutadiene as Knoevenagel alkene intermediate which could be assembled intera-molecularly to tethered alkene in later stage and formed titled polycyclic heterocycles. All the compounds were screened against three Gram +ve, three Gram –ve and M. Tuberculosis H37RV bacteria, as well as two funguses. In many cases, notable bioactivity was observed, in comparison with standard drugs used. FRAP (ferric reducing anti-oxidant power) assay was also employed to determine Anti-oxidant activity of compounds.

Keywords: Solvent-free reaction, DKHDA reaction, Quinoline–heterocycles, Pyrazol–heterocycles, Antimicrobial activity

INTRODUCTION

Translation of conventional method which consumes a lot of solvents into a one which avoids use of solvents, producing less environmental impact, is of growing interest in modern synthetic organic chemistry [1]. Generation of wastes associated with both the industrial and academic practices, in chemical laboratory, is now considered as one of the key issues to be carefully addressed before establishing new synthetic methodologies [2]. Besides, daily requirement of non-renewable solvents for performing conventional method threaten to diminish our fossil fuel oil to a larger extent, leading ultimately to an ecological imbalance in terms of natural distribution of materials. Green methodologies, therefore, attracted interest of many synthetic organic chemists, and so considerable amount of works in this context appeared and happened in last couple of decades [1a]. As a result, number of environmentally friendly procedures came into existence to achieve the target molecules, and solvent-free method among them particularly played a key role in development of many synthetic transformations [2a]. Some notable transformations include reduction of ketone and aldehyde in sodium borohydride as catalyst [3], Beginelli–type reactions [4], Knoevenagel condensation [5], cyanosilylation of carbonyl compounds [6], Michael–addition chemistry [7], Domino Oxa-Michael-Aldol Reaction [8], Cross coupling reactions [9] and Diels—Alder reaction [10].

Quinoline and quinoline-based heterocycles are often found in nature, being common framework of number of bioactive heterocycles [11]. Powerful bacteriostatic and anti-inflammatory nature [12] of chromeno-fused quinolines revealed glucocorticoidal property [13]. Effective in Alzheimer's disease [14], few heterocycles of this family also acted as estrogen receptor β-selective ligands [15]. Dihydrochromenoquinolines, particularly, are well-known robust pharmacophores for selective progesterone receptor modulators (SPRMS), having progestational activity [16]. Others are effective in fertility regulation or breast cancer treatment. Recent report of Maalej on scaffolds belonging to this class showed selective, potent and mixed type EeAChE inhibitions [17]. Other candidates include Anti-cancer agent, MT477, with protein kinase C (PKC) isoform inhibitory action [18], 3,4-dihydro-2H-thiopyrano-[2,3-b]quinoline with metabotropic glutamate receptor antagonistic property [19] and 2H-thiopyrano[2,3-b]quinoline-2-carboxylic acid with a strong antioxidant property [20].

Apart from quinoline-based frameworks, pyrano[2,3-c]pyrazole also gained a much prominence in recent years as a central skeleton of many compounds known for their antimicrobial [21], insecticidal [22], anti-inflammatory [23] and molluscicidal activities [24]. Other examples of pyrazolo-fused heterocycles includes antidepressant 2,3-dihydrochromeno[4,3-d]pyrazolo-[3,4-b]pyridine-1,6-diones [25a-b], pyrano-fused pyrazol with photochemical property [25c] and 4,4'-(arylmethylene)bis(1H-pyrazol-5-ols) with remarkable anti-inflammatory, gastric secretion stimulatory, antibacterial, and antifilarial activities [25d].

In addition to just fusion envisioned between heterocyclic units, angular fusion between them preparing fused-ring systems as conjugates of heterocycles with other bioactive ring with somewhat rigid skeleton is of special interest, as class of these compounds found important applications in medicinal chemistry. Naturally occurring cannabicyclol [26], mahanimbine [27], steroids [28], and thyrsiferol [29] are important examples of angularly fused polycyclic ring-systems. Bioactive heterosteroids [30-32] are other examples of this family,

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have significantly improved biological function.

In view of above, thus quinoline– and pyrazol–heterocycles, all of which possess angular methyl group, are worth studying and have high degree of medicinal importance. In present work, we demonstrate the catalyst- and solvent-free version of affording angular quinoline– and pyrazol–annulated heterocycles, and their biological evaluation. All heterocycles are anticipated to show interesting and new biological function, with angular methyl group.

RESULTS AND DISCUSSION

Requisite aldehyde– and ketone–based substrates; 8-methyl/9-chloro-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-thiopyrano[2,3-b]-quinoline-3-carbaldehydes 2a-c and O-prenylated/ allylated-acetophenones/propiophenones 3a-h, were obtained by treating 2-mercaptoquinoline-3-carbaldehyde with citral in refluxing xylene [33], and reacting O-hydroxyacetophenone/ propiophenone with prenyl/allyl-bromide in anhydrous potassium carbonate in DMF, respectively [34], reported elsewhere. Combination of substrates; 2a-c and 3a-h, each with respective pyrazolone 1a-c, afforded polyheterocycles 4a-i and 5a-n, respectively, in higher yield, within 5–8 h under solvent free environment at 120 ℃. The present protocol is a new version of synthesizing typical quinoline- and pyrazol-heterocycles reported elsewhere [33-34] under catalyst– and solvent–free condition, and is highly advantageous ecologically. Entire synthetic sequence is outlined in Scheme 1, and products formed at the end of the reaction are defined in Table 1, with their physical constants.

Scheme 1: Synthesis of quinoline (4a–i)– and pyrazol (5a–n)–heterocycles:

Reagent and condition; (a) Solid state melt reactions at 120 ℃

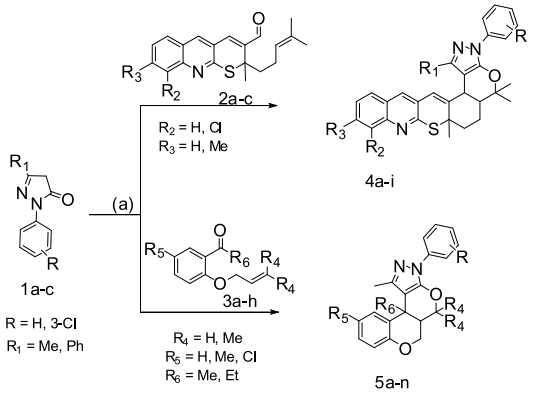

Table 1: Synthesis of quinoline– (4a–i) and pyrazol– (5a–n) heterocycles

Entry	Product	R	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	M.P(℃)
1	4a	H	Me	H	H	-	—	—	91	260—262
2	4b	3-Cl	Me	H	H	—	—	—	88	254—256
3	4c	H	Ph	H	H	—	—	—	91	234—236
4	4d	H	Me	H	Cl	—	—	—	91	136—138
5	4e	3-Cl	Me	H	Cl	—	—	—	90	170—172
6	4f	H	Ph	H	Cl	—	—	—	86	144—146
7	4g	H	Me	Me	H	—	—	—	93	146—148
8	4h	3-Cl	Me	Me	H	—	—	—	90	210—212
9	4i	H	Ph	Me	H	—	—	—	88	188—190
10	5a	H	—	—	—	H	H	Me	67	152—154
11	5b	3-Cl	—	—	—	H	H	Me	63	146—148
12	5c	H	—	—	—	H	Me	Me	70	138—140
13	5d	3-Cl	—	—	—	H	Me	Me	63	142—144
14	5e	H	—	—	—	H	Cl	Me	60	134—136
15	5f	3-Cl	—	—	—	H	Cl	Me	61	110—112
16	5g	H	—	—	—	H	H	Et	39	132—133
17	5h	H	—	—	—	Me	H	Me	70	170—172
18	5i	3-Cl	—	—	—	Me	H	Me	68	148—150
19	5j	H	—	—	—	Me	Me	Me	71	212—214
20	5k	3-Cl	—	—	—	Me	Me	Me	67	168—170
21	5l	H	—	—	—	Me	Cl	Me	64	248—250
22	5m	3-Cl	—	—	—	Me	Cl	Me	67	182—184
23	5n	H	—	—	—	Me	H	Et	46	145—147

The spectroscopic data of quinoline–heterocycles 4a-i support cis-fusion between central rings, well with proposed structures. In 1H NMR spectra, two singlets appeared at δ 1.2–1.5 ppm and a singlet at δ 1.5–1.6 ppm, show 5-Me and 7a-Me protons respectively. A doublet appeared in the δ 3.7–4.1 ppm range with coupling constant J = 6.8–8.8 Hz can be assigned to proton 15b, and J value suggest cis fusion between central rings occurred via less sterically hindered endo-E-syn transition state. A multiplet found at δ 2.3–2.5 ppm is due to 5a protons. A singlet at δ 6.2–6.5 ppm can be assigned to 15-CH protons. The characteristic IR band appeared in the V 1105–1138 cm-1 range indicates pyranyl C–O–C linkage. A band in the V 650–710 cm-1 range conforms the C–S–C of the thiopyran unit. The mass spectrometry data of the heterocycles are matched correctly with the calculated molecular weights.

Pyrazol-heterocycles, 5a-n, contains cis-fused geometries. In FT—IR, bands in the 3050—3010 cm-1 range and 3000—2850 cm-1 range are due to V sp2 C—H and V sp3 C—H. A characteristic band due to cyclic ether linkage appeared in the 1220—1240 cm-1 region, so supporting pyran ring formation. V sp2 C—N gave a band in 1575—1600 cm-1 range.

1H NMR spectra of O-allyloxyacetophenone-derived polyhetrocycles, 5a-f, showed two singlets; one in at δ 1.80—1.82 ppm and second at δ 2.59—2.71 ppm, due to angular and pyrazole-attached Me protons respectively. A multiplate at δ ~2.16 ppm can be assigned to a single CH proton. Two dd; one at δ ~4.53 (J = 11.2, 3.6 Hz) ppm and second at δ 4.58 (J = 12.0, 2.8 Hz) ppm value, can be attributed to protons H5 and H6. Other two protons, H5' and H6' gave a multiplate at δ ~4.27 ppm. In 13C NMR spectra of 5a-f, pyrazole-attached and angular Me protons gave peaks in the ranges; δ 16—17 ppm and δ 29—30 ppm respectively. The CH carbon gave a characteristic peak at δ ~37.85 ppm, and O—CH2 carbons, one at δ ~62.86 ppm and second at δ ~69.07 ppm.

1H NMR spectra of compounds, 5i-m, derived from O-prenylatedacetophenones, showed angular Me as a singlet in up field at δ 1.05—1.11 ppm due to inductive effect of two Me groups at C—5, a doublet at ~δ 1.95 ppm (J = 3.2 Hz) due to the CH proton. Two O—CH2 protons gave ddd at δ ~4.43 (J = 12.8, 4.0, 1.2 Hz) and 4.72 (J = 12.6, 4.4, 2.0 Hz) ppm. 13C NMR spectra of compounds showed two peaks; one at around δ 16.78 ppm and second at δ 22.75 ppm, are attributed to pyrazole-attached and angular Me protons, with angular Me shift observed to up field due to inductive effect of two Me groups. Due to CH proton shift down field, it gave a peak at δ ~47.11 ppm. A peak at δ 61.95 ppm assigns to O—CH2 fragment. Tertiary carbon observed down field at δ ~82.72 ppm. Two bridge–head methylene protons present in propiophenone-based compounds, 5g and 5n, are appeared as multiplets at δ 2.03–2.39 ppm, and corresponding carbon at δ ~33 ppm.

All polyheterocycles, 4a-i and 5a-n, have had their biological profiles unknown, they were screened in vitro against three Gram-positive (Streptococcus pneumoniae, Clostridium tetani, Bacillus subtilis) and three Gram-negative (Salmonella typhi, Vibrio cholerae, Escherichia coli) bacteria, for their antibacterial activities, and against fungi Aspergillus fumigatus and Candida albicans, for their antifungal activity, employing macro-broth dilution assay. Antitubercular activity was also carried out testing compounds against M. Tuberculosis H37RV bacteria. Finally, Benzie and Strain's modified method was employed to determine ferric reducing anti-oxidant power (FRAP) of all heterocycles, for anti-oxidant activity. Table 2 shows biological screening test results. It clearly shows majority of heterocycles are rather good anti-bacterial than anti-fungal in nature, particularly screening against Gram +ve Bacillus subtilis and Clostridium tetani bacteria, with the potency equivalent to at least one of the reference drugs, and mostly Ampicillin. The compound 4h reveals both Chloramphenicol and Ciprofloxacin drugs in activity against Gram +ve Bacillus subtilis bacteria, indicating that it has higher antibacterial resistivity than Ampicillin. Compounds 4b, 4e, 4g, 5b, 5d, 5i and 5m, on the other, exhibited, more-potent-than-Ampicillin, Ciprofloxacin like activity against Gram +ve Clostridium tetani bacteria, with MIC value of 62.5 µg/mL. Compound 4b among them additionally showed good resistance against Gram –ve Escherichia coli bacteria, and thus resembles another more potent standard drug Chloramphenicol in activity, in comparison with Ampicillin. Structurally, 1-(3-ClPh)-3-methyl-5-pyrazolone–derived polyheterocycles showed promising anti-bacterial profiles.

Compounds 4a, 4c, 4f, 4h. 4i, 5a, 5c, 5e, 5i, 5j and 5l showed good resistivity against Candida albicans fungus, revealing anti-fungal activity directly comparable with standard drug Griseofulvin. Again 1-(3-ClPh)-3-methyl-5-pyrazolone–derived polyheterocycles in majority of cases relate this property.

All the compounds were screened against M. Tuberculosis H37RV bacteria, and compounds 4c, 4e, 5g and 5k among them revealed good anti-tubercular properties, most of which contain central pyrano-pyran framework attached to methyl substituent, in addition to a bridge-head methyl or ethyl group.

Although the anti-oxidant activity of majority of compounds is poor, compounds such as 5d, 5e, 5f and 5h, derived from acetophenones-based substrates, revealed good anti-oxidant property with the FRAP value lying above 100 mM/100 g sample.

Table 2: Antibacterial, antifungal, antitubercular and antioxidant activities of compounds 4a-i and 5a-n

Product	Antimicrobial Activity (MIC, $\mu g mL^{-1}$)								Anti TB[a] % Growth of inhibition	Anti-oxidant[b] activity FRAP Value[c]
	Gram positive bacteria			Gram negative bacteria			Fungi			
	B.s.	*C.t.*	*S.p.*	*E.c.*	*S.t.*	*V.c.*	*A.f.*	*C.a.*		
4a	**100**	200	200	250	**100**	**100**	>500	500	78	78.60
4b	**100**	**125**	250	**62.5**	200	500	500	>500	15	88.70
4c	200	250	200	200	250	200	500	**250**	**89**	76.60
4d	**125**	200	200	**125**	**125**	500	250	>500	74	80.64
4e	**100**	**125**	250	**125**	250	200	>500	>500	81	74.59
4f	250	200	200	250	**125**	250	>500	500	20	90.72
4g	250	**100**	**100**	250	200	**100**	>500	>500	45	96.77
4h	**62.5**	200	200	500	500	200	500	**250**	44	70.56
4i	250	250	250	250	200	**100**	500	**250**	49	78.62
5a	250	200	**100**	**125**	250	200	>500	500	51	46.50
5b	**100**	**125**	**100**	200	250	250	500	>500	57	68.66
5c	200	200	200	500	500	250	>500	500	76	74.80
5d	200	**100**	**125**	**125**	250	200	250	>500	20	220.05
5e	**100**	200	200	**100**	**100**	250	>500	250	54	194.32
5f	200	200	250	250	250	200	>500	>500	46	112.79
5g	250	250	200	**100**	250	100	>500	>500	**84**	45.11
5h	500	500	500	**100**	250	500	500	>500	58	173.94
5i	200	**100**	**150**	200	**100**	250	>500	250	73	73.61
5j	250	200	250	500	250	**125**	>500	500	13	54.22
5k	200	200	200	**100**	500	250	>500	>500	**91 (125)**	92.81
5l	500	200	500	200	250	200	>500	500	41	55.01
5m	250	**100**	**100**	200	**100**	500	500	>500	45	111.61
5n	500	250	250	500	200	250	>500	>500	76	42.15
[A]	1	5	0.5	0.05	5	5	-	-	-	
[B]	250	250	100	100	100	100	-	-	-	
[C]	50	50	50	50	50	50	-	-	-	
[D]	50	100	50	25	25	25	-	-	-	
[E]	100	50	10	10	10	10	-	-	-	
[F]	-	-	-	-	-	-	100	100	-	
[G]	-	-	-	-	-	-	100	500	-	
[H]	-	-	-	-	-	-	-	-	99	

S.p.: Streptococcus pneumoniae, C.t.: Clostridium tetani, B.s.: Bacillus subtilis, S.t.: Salmonella typhi, Vc.: Vibrio umigat, E.c.: Escherichia coli, A.f.: Aspergillus fumigates, C.a.: Candida albicans, [A]:Gentamycin, [B]: Ampicillin [C]: Chloramphenicol, [D]: Ciprofloxacin, [E]: Norfloxacin, [F]: Nystatin, [G]: Griseofulvin, [H]: Isoniazide; [a]Concentration of compounds used against M. tuberculosis H37RV = 250 µg/mL and standard antimicrobials used: Isoniazide (0.20 µg/mL). bConcentration of compounds = 200 µg/mL and standard: A.A. (ascorbic acid) = 176 µg/mL, cA.A. mM/100 g sample

CONCLUSION

Thus, we demonstrated synthesis of some quinoline- and pyrazol-heterocycles via DKHDA reaction in catalyst- and solvent-free condition at 120 o C. Avoidance of catalyst and solvent practiced in the present work is a main advantage of this new method, fulfills many green chemistry principles. Biological screening test results revealed many compounds as new bioprofiles and it could be seen that compounds have rather good anti-bacterial than antigungal activity. Compounds 4b and 4h showed strong resistivity against Gram –ve Escherichia coli and Gram +ve Bacillus subtillis bacteria, respectively, with MIC of 62.5 µg/mL. Generally, polyhetrocycles derived from 1-(3-ClPh)-3-methyl-5-pyrazolone unit showed good anti-microbial profiles.

EXPERIMENTAL

General

All solvents and chemical reagents were used as supplied from commercial sources. All recorded melting points are uncorrected. IR spectra were recorded in KBr on a Shimadzu FT-IR 8401 spectrometer and are reported in wave numbers (cm-1). 1H NMR and 13C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for 1H NMR and 100 MHz for 13C NMR in CDCl3 as both solvent and reference. Chemical shifts are expressed in parts per million (ppm, d) and referenced to the residual protic solvent. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as s, for singlet; d, for doublet; t, for triplet; q, for quartet; br, for broad; m, for multiplet; comp, for complex multiplet. The degree of substitution (C, CH, CH2, and CH3) was determined by the DEPT-135 method. The ESI mass data were taken on a Shimadzu LCMS- 2010 spectrometer. Elemental analyses (% C, H, N) were carried out by a Perkin-Elmer 2400 series-II elemental analyzer (Perkin- Elmer, USA). TLC was performed on Merck 60 F254 pre-coated silica plates, and spots were detected under a UV lamp (254 nm, 366 nm), or by dipping into a permanganate solution (prepared by dissolving 3 g KMnO4, 20 g K2CO3 and 5 mL, 5% NaOH in 300 mL H2O), an anisaldehyde solution (prepared by dissolving 3% p-methoxybenzaldehyde and 1% H2SO4 in MeOH) or 2,4-dinitro phenyl hydrazine solution (prepared by dissolving 12 g 2,4-DNP and 6 mL conc. H2SO4 in a mixture of 8 mL water and 20 mL EtOH) followed by heating.

General procedure for synthesis of quinoline based (4a–i) & pyrazole based (5a–n) polyheterocycles.

In a round-bottom flask, a mixture containing equal amount 5-pyrazolones derivaties 1a–c and quinoline based carbaldehydes 2a–c or O-allkenylated acetophenones derivatives 3a-h was heated at 120 ℃ without catalyst and solvent mediam. Reaction was continued monitored by TLC; reaction was continued until the all substrate was disappeared. Remaining crude product was then subjected to column chromatography, employing an ethyl acetate/hexane (3:7) eluent, affording compounds 4a–i or 5a–n in pure product with excellent yields.

Spectroscopic data of some selected compounds

3-(3-chlorophenyl)-1,5,5,7a-tetramethyl-5,5a,6,7,7a,15b-hexahydro-3H-pyrazolo[4'',3'':5',6'] pyrano[4',3':5,6]thiochromeno[2,3-b]quinoline(4b); yield 88%; mp 254–256 ℃; IR (νmax, cm-1): 670, 752, 1125, 1392, 1515, 1598, 1652, 2926, 2950, 2979, 3062; 1H NMR (400 MHz, CDCl3): δ 1.32 (s, 3H, 5–CH3), 1.47 (s, 3H, 5–CH3), 1.68 (s, 3H, 7a–CH3), 1.77–2.11 (m, 4H, 6 & 7–CH2), 2.38 (s, 3H, 1– CH3), 2.41–2.52 (m, 1H, 5a–H), 4.02 (d, 1H, J = 7.2 Hz, 15b–H), 6.56 (s, 1H, 15–H), 7.22–7.94 (m, 9H, Ar–H); 13C NMR (100 MHz, CDCl3): δ 13.52, 20.88, 21.96, 28.47, 30.22, 31.98, 33.62, 41.15, 48.19, 85.09, 117.91, 120.09, 122.12, 125.23, 125.65, 126.22, 126.78, 127.19, 128.65, 130.15, 132.35, 134.85, 135.23, 143.50, 147.67, 147.98, 159.69 (Ar-C); ESI-MS (m/z): 513.16 (M) +, Anal Calcd for C30H28ClN3OS: C, 70.09; H, 5.49; N, 8.17; Found: C, 69.91; H, 5.53; N, 8.05.

11-chloro-5,5,7a-trimethyl-1,3-diphenyl-5,5a,6,7,7a,15b-hexahydro-3H-pyrazolo[4'',3'':5',6'] pyrano[4',3':5,6]thiochromeno[2,3-b]quinoline(4f); yield 86%; mp 144–146 ℃; IR (νmax, cm-1): 675, 762, 780, 896, 945, 1079, 1135, 1394, 1496, 1510, 1603, 1615, 2858, 2925, 3070; 1H NMR (400 MHz, CDCl3): δ 1.19 (s, 3H, 5–CH3), 1.48 (s, 3H, 5–CH3), 1.58 (s, 3H, 7a–CH3), 2.09–2.16 (m, 4H, 6&7–CH2), 2.41 (s, 4H, 1–CH3), 2.45–2.49 (m, 1H, 5a–H), 3.85 (d, 1H, J = 8.4 Hz, 15b–H), 6.36 (s, 1H, 15–H), 7.11–7.89 (m, 9H, Ar–H) 1.32 (s, 3H, 5–CH3), 1.48 (s, 3H, 5–CH3), 1.68 (s, 3H, 7a–CH3), 1.77–2.07 (m, 4H, 6 & 7–CH2), 2.41–2.56 (m, 1H, 5a–H), 4.01 (d, 1H, J = 8.4 Hz, 15b–H), 6.56 (s, 1H, 15–H), 6.89–7.99 (m, 14H, Ar–H); 13C NMR (100 MHz, CDCl3): δ 14.24, 21.22, 22.56, 28.31, 31.32, 32.15, 33.49, 41.25, 48.17, 85.18, 105.40, 116.85, 117.54, 120.58, 124.87, 125.12, 127.59, 127.89, 127.95, 128.02, 128.22, 128.80, 136.66, 138.50, 140.03, 141.07, 148.41, 150.10, 152.58, 157.47(Ar-C); ESI-MS (m/z): 575.18 (M) +, Anal Calcd for C35H30ClN3OS: C, 72.96; H,5.25; N, 7.29; Found: C, 73.10; H, 5.20; N, 7.35.

10-Chloro-1,11b-dimethyl-3-phenyl-3,5a,6,11b-tetrahydro-5H-chromeno[4',3':4,5]pyrano[2,3-c] pyrazole(5e); yield 60%; m.p.: 134–136℃; IR (νmax, cm-1) 683, 755, 820, 840, 1041, 1092, 1226, 1444, 1481, 1563, 1590, 2928, 2969; 1H NMR (400 MHz, CDCl3): δ 1.80 (s, 3H, angular Me), 2.16 (m, 1H, H5a), 2.59 (s, 3H, pyrazole Me), 4.23 (m, 2H, H5 and H6), 4.44 (dd, J = 11.2, 3.2 Hz, H6'), 4.52 (dd, J = 11.8, 3.2 Hz, H5'), 6.74–7.51 (m, 8H, Ar-H); 13C NMR (100 MHz, CDCl3): δ 16.40 (pyrazole Me), 29.52 (angular Me), 34.30 (C-11b), 37.80 (C-5a), 63.19 (C-5), 68.81 (C-6), 100.79, 117.76, 120.88, 125.71, 125.83, 127.45, 127.91, 128.97, 130.88, 138.76, 146.55, 148.18, 151.32 (Ar-C); ESI-MS (m/z): 366.84 [M + H+]; Anal Calcd for C21H19ClN2O2: C, 68.76; H, 5.22; N, 7.64; Found: C, 68.52; H, 5.06; N, 7.88.

10-Chloro-1,5,5,11b-tetramethyl-3-phenyl-3,5aR,6,11bS-tetrahydro-5H-chromeno[4',3':4,5] pyrano[2,3-c]pyrazole(5l); yield 64%; m.p.: 248–250℃; IR (νmax, cm-1) 674, 764, 828, 858, 1041,

1088, 1229, 1439, 1485, 1554, 1586, 2922, 2964; 1H NMR (400 MHz, CDCl3): δ 1.10 (s, 3H, angular Me), 1.65 (s, 3H, Me-5), 1.76 (s, 3H, Me-5'), 1.98 (d, J = 3.2, 1H, H5a), 2.70 (s, 3H, pyrazole Me), 4.42 (td, J = 12.8, 1.6 Hz, 1H, H6), 4.69 (ddd, J = 12.6, 4.4, 2.0 Hz, H6'), 6.69–7.78 (m, 8H, Ar-H); 13C NMR (100 MHz, CDCl3): δ 16.78 (pyrazole Me), 22.74 (angular Me), 29.14 (Me-5), 31.94 (Me-5'), 33.80 (C-11b), 46.75 (C-5a), 62.07 (C-6), 82.58 (C-5), 100.60, 117.70, 120.70, 125.54, 125.61, 127.37, 127.70, 128.85, 130.86, 138.63, 146.47, 148.14, 151.25 (Ar-C); ESI-MS (m/z): 394.89 [M + H+]; Anal Calcd for C23H23ClN2O2: C, 69.95; H, 5.87; N, 7.09; Found: C, 69.81; H, 6.07; N, 7.28.

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