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SYNTHESIS OF SOME FLUORINATED CHROMENE DERIVATIVES BY COUPLING OF NEBULIC ACID AND AMINOBENZOTRIFLUORIDES

RESEARCH ARTICLE

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ABSTRACT

The paper constitutes the research performed to developed new fluorinated chromene derivatives by coupling reaction of respective substituted aminobenzotrifluoride compounds and nebulic acid using suitable coupling reagents. The reaction is clean which enable too easy workup and good yield.

Keywords: *Amino benzotrifluorides, nebulic acid, coupling reagents.*

INTRODUCTION

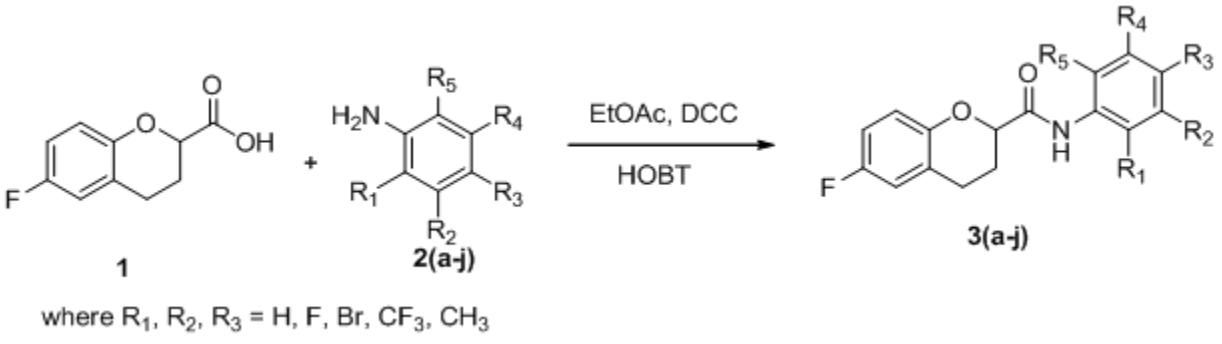
Fluorinated chromene compounds which may be useful in medicinal field. Since fluorine atom possesses high electronegativity it has hydrophilic character. Also C-F bond is much stronger than C-H which increases the bioavailability and half-life of the compounds.

Many compounds contain chromene ring derivatives exhibit broad spectrum of biological activity [1–4]. Recently, beginning of fluorine atoms into organic compounds has been regarded as one of the best ways for the improvement or alteration of their novel biological activities [5, 6]. It was found and confirmed that the trifluoromethyl (CF_3) group, regarded as a pseudo-halogen, impart exclusive biological activity [7, 8]. It is well known that $–CF_3$ group plays important role in medicinal chemistry as it enhances the efficacy by promoting electrostatic interaction with targets, improving cellular membrane permeability and increasing resistance towards oxidative metabolism of the drug.

Also, new fluoro-substituted analogs are currently being designed with the aim of increasing metabolic stability of the molecule. As it is known in the literature, the incorporation of fluorine enhances therapeutic efficacy and improves pharmacological properties in bioactive molecules. The presence of fluorine often leads to increased lipid solubility, enhancing rates of absorption and transport of drugs in vivo.

REACTION SCHEME

The synthesis scheme employed to obtain the target compounds.



where R_1, R_2, R_3 = H, F, Br, CF_3, CH_3

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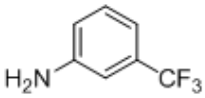
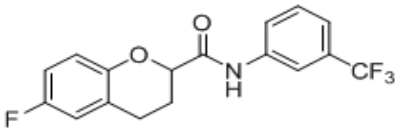
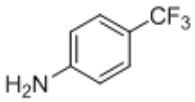
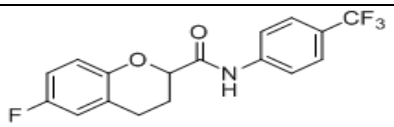
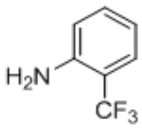
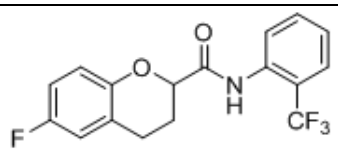
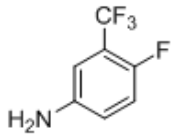
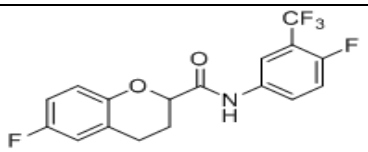
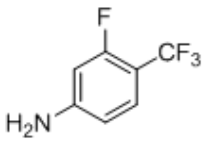
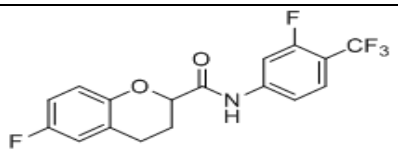
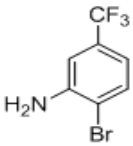
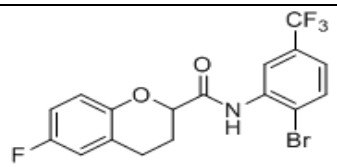
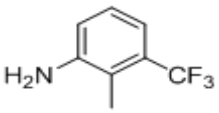
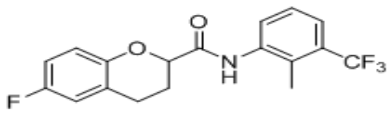
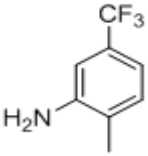
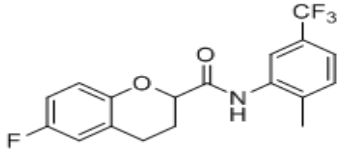
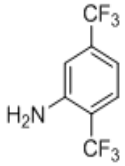
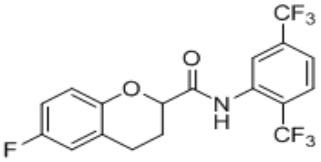
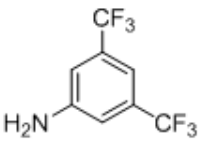
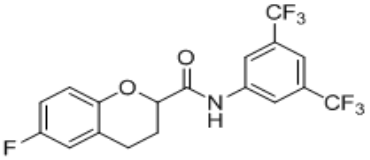
Scheme-1 reagents and condition (1) Dicyclohexylcarbodimide and 1-hydroxybenzotriazole both 1.05Eq, dry MDC/EtOAc, 6-12 hrs at reflux.

Chromene derivatives 3(a-j) are synthesized by coupling reaction between different substituted aminobenzotrifluorides 2(a-j) and nebulic acid (1). N,N'-Dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) are used as a coupling reagent. N,N'-Dicyclohexylcarbodiimide urea is formed as a side product during reaction which can remove by filtration.

RESULTS AND DISCUSSION

Table-1: Chromene derivatives

Entry	Aniline	Product	Time (h)	Yield (%)	MP (^{0}C)
a			7	66	189-192
b			6	69	197-200
c			7	64	176-179
d			12	61	172-175
e			10	62	180-183
f			8	66	218-221
g			11	60	212-215
h			9	56	208-211
I			8	61	123-126
j			10	54	115-118

CONCLUSION

The process for the synthesis of chromene derivatives is relatively simpler. The reagents used are also available commercially and easy to handle. Also the process is easily scalable and commercially feasible as all the compounds are synthesize in good yields. The synthesized compounds are characterized by Mass, IR spectra and ^{1}H NMR.

EXPERIMENTAL SECTION

General. All starting materials and solvents were purchased from common commercial suppliers and were used freshly purified by standard procedures if required. Reactions were monitored by TLC using silica-gel coated plates and ethyl acetate/hexanes solutions as the mobile phase, spots were located by iodine and UV. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}). ^{1}H NMR spectra were obtained on a FT-NMR Bruker Ultra ShieldTM (400 MHz) instrument as DMSO-d_6 solutions and the chemical shifts are expressed as units with Me_4Si as the internal standard. Mass spectra were recorded on direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument.

General procedure for synthesis of Chromene derivatives [3(a-j)]

Nebulic acid [1] was dissolve in fresh anhydrous ethyl acetate (8.0 Volumes), N,N'-Dicyclohexylcarbodiimide (1.2 Eq) was added followed by 1-hydroxybenzotriazole (0.5 Eq) at 0 ^{o}C. After addition reaction mixture was allowed to warm up to 25-30 ^{o}C and was stirred at same temperature for 1-2 hrs. Then different substituted aminobenzotrifluorides (1.2 Eq) [2(a-j)] were added dropwise and further reaction mixture was allowed to stirred at 25-30 ^{o}C for 6-12 hrs. Completion of reaction was monitored by TLC, after that reaction mixture was cooled and N, N'-Dicyclohexylcarbodiimide urea salt was filtered. Filtrate was distilled to remove the solvent, desire compound was purified with flash column chromatography.

1. 6-fluoro-N-(3-(trifluoromethyl)phenyl)chroman-2-carboxamide (3a)
^{1}H NMR (400 MHz, DMSO): δ = 8.69 (s, 1H), 8.21 (d, *J* = 1.4 Hz, 1H), 7.69 (dd, *J* = 8.2, 5.4 Hz, 1H), 7.42-7.39 (m, 2H), 6.91 (dd, *J* = 8.4, 4.6 Hz, 1H), 6.83 (m, 1H), 6.77 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.58 (dd, *J* = 9.4, 3.2 Hz, 1H), 2.88-2.65 (m, 2H), 2.43 (m, 1H), 2.10 (m, 1H); IR (cm^{-1}): 3248 (N-H), 3017 (C-H aromatic ring), 2952 (C-H), 2846 (C-H), 1657 (C=O), 1422 (C=C), 1346 (C-H), 1321 (C-H), 1272 (C-N), 1087 (C-O), 1019 (C-F) cm^{-1}. Yield: 66%; mp 189-192 ^{o}C; MS (m/z): 339 (M+); Anal. calcd for $C_{17}H_{13}F_4NO_2$: C, 60.18; H, 3.86; F, 22.40; N, 4.13; O, 9.43; Found: C, 60.12; H, 3.78; F, 22.29; N, 4.09; O, 9.28.

2. 6-fluoro-N-(4-(trifluoromethyl)phenyl)chroman-2-carboxamide (3b)
IR (cm^{-1}): 3256 (N-H), 3024 (C-H aromatic ring), 2961 (C-H), 2821 (C-H), 1654 (C=O), 1431 (C=C), 1364 (C-H), 1319 (C-H), 1281 (C-N), 1075 (C-O), 1023 (C-F) cm^{-1}. Yield: 69%; mp 197-200 ^{o}C; MS (m/z): 339 (M+); Anal. calcd for $C_{17}H_{13}F_4NO_2$: C, 60.18; H, 3.86; F, 22.40; N, 4.13; O, 9.43; Found: C, 60.12; H, 3.79; F, 22.38; N, 4.10; O, 9.37.

3. 6-fluoro-N-(2-(trifluoromethyl)phenyl)chroman-2-carboxamide (3c)
IR (cm^{-1}): 3229 (N-H), 3014 (C-H aromatic ring), 2957 (C-H), 2838 (C-H), 1658 (C=O), 1438 (C=C), 1351 (C-H), 1319 (C-H), 1278 (C-N), 1084 (C-O), 1015 (C-F) cm^{-1}. Yield: 64%; mp 176-179 ^{o}C; MS (m/z): 339 (M+); Anal. calcd for $C_{17}H_{13}F_4NO_2$: C, 60.18; H, 3.86; F, 22.40; N, 4.13; O, 9.43; Found: C, 60.14; H, 3.78; F, 22.35; N, 4.15; O, 9.34.

4. 6-fluoro-N-(4-fluoro-3-(trifluoromethyl) phenyl) chroman-2-carboxamide (3d)
IR (cm^{-1}): 3243 (N-H), 3041 (C-H aromatic ring), 2943 (C-H), 2817 (C-H), 1652 (C=O), 1446 (C=C), 1328 (C-H), 1308 (C-H), 1286 (C-N), 1124 (C-O), 1025 (C-F) cm^{-1}. Yield: 61%; mp 172-175 ^{o}C; MS (m/z): 357 (M+); Anal. calcd for $C_{17}H_{12}F_5NO_2$: C, 57.15; H, 3.39; F, 26.59; N, 3.92; O, 8.96; Found: C, 57.12; H, 3.27; F, 26.43; N, 3.84; O, 8.79.

5. 6-fluoro-N-(3-fluoro-4-(trifluoromethyl)phenyl)chroman-2-carboxamide (3e)
IR (cm^{-1}): 3261 (N-H), 3032 (C-H aromatic ring), 2932 (C-H), 2840 (C-H), 1658 (C=O), 1429 (C=C), 1332 (C-H), 1311 (C-H), 1278 (C-N), 1131 (C-O), 1009 (C-F) cm^{-1}. Yield: 62%; mp 180-183 ^{o}C; MS (m/z): 357 (M+); Anal. calcd for $C_{17}H_{12}F_5NO_2$: C, 57.15; H, 3.39; F, 26.59; N, 3.92; O, 8.96; Found: C, 57.16; H, 3.32; F, 26.54; N, 3.88; O, 8.85.

6. N-(2-bromo-5-(trifluoromethyl)phenyl)-6-fluorochroman-2-carboxamide (3f)
IR (cm^{-1}): 3253 (N-H), 3021 (C-H aromatic ring), 2948 (C-H), 2836 (C-H), 1652 (C=O), 1448 (C=C), 1339 (C-H), 1316 (C-H), 1274 (C-N), 1114 (C-O), 1016 (C-F) cm^{-1}. Yield: 66%; mp 218-221 ^{o}C; MS (m/z): 417 (M+); Anal. calcd for $C_{17}H_{12}BrF_4NO_2$: C, 48.83; H, 2.89; Br, 19.11; F, 18.17; N, 3.35; O, 7.65; Found: C, 48.76; H, 2.78; Br, 19.06; F, 18.12; N, 3.37; O, 7.54.

7. 6-fluoro-N-(2-methyl-3-(trifluoromethyl)phenyl)chroman-2-carboxamide (3g)
^{1}H NMR (400 MHz, DMSO): δ = 8.86 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.0, 7.4 Hz, 1H), 6.91 (dd, *J* = 8.4, 4.6 Hz, 1H), 6.84 (m, 1H), 6.78 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.59 (dd, *J* = 9.0, 3.3 Hz, 1H), 2.88-2.64 (m, 2H), 2.42 (m, 1H), 2.19 (s, 3H), 2.10 (m, 1H); IR (cm^{-1}): 3246 (N-H), 3039 (C-H aromatic ring), 2937 (C-H), 2813 (C-H), 1657 (C=O), 1432 (C=C), 1338 (C-H), 1317 (C-H), 1278 (C-N), 1127 (C-O), 1016 (C-F) cm^{-1}. Yield: 60%; mp 212-215 ^{o}C; MS (m/z): 353 (M+); Anal. calcd for $C_{18}H_{15}F_4NO_2$: C, 61.19; H, 4.28; F, 21.51; N, 3.96; O, 9.06; Found: C, 61.08; H, 4.32; F, 21.46; N, 3.83; O, 9.02.

8. 6-fluoro-N-(2-methyl-5-(trifluoromethyl)phenyl)chroman-2-carboxamide (3h)
IR (cm^{-1}): 3237 (N-H), 3032 (C-H aromatic ring), 2927 (C-H), 2816 (C-H), 1656 (C=O), 1443 (C=C), 1321 (C-H), 1310 (C-H), 1276 (C-N), 1131 (C-O), 1023 (C-F) cm^{-1}. Yield: 56%; mp 208-211 ^{o}C; MS (m/z): 353 (M+); Anal. calcd for $C_{18}H_{15}F_4NO_2$: C, 61.19; H, 4.28; F, 21.51; N, 3.96; O, 9.06; Found: C, 61.12; H, 4.17; F, 21.46; N, 3.79; O, 9.02.

9. N-(2, 5-bis(trifluoromethyl)phenyl)-6-fluorochroman-2-carboxamide (3i)
IR (cm^{-1}): 3241 (N-H), 3034 (C-H aromatic ring), 2951 (C-H), 2817 (C-H), 1659 (C=O), 1453 (C=C), 1332 (C-H), 1317 (C-H), 1272 (C-N), 1109 (C-O), 1018 (C-F) cm^{-1}. Yield: 61%; mp 123-126 ^{o}C; MS (m/z): 407 (M+); Anal. calcd for $C_{18}H_{12}F_7NO_2$: C, 53.08; H, 2.97; F, 32.65; N, 3.44; O, 7.86; Found: C, 53.11; H, 2.78; F, 32.58; N, 3.42; O, 7.76.

10. N-(3, 5-bis(trifluoromethyl)phenyl)-6-fluorochroman-2-carboxamide (3j)
^{1}H NMR (400 MHz, DMSO): δ = 8.95 (s, 1H), 8.32 (d, *J* = 2.2 Hz, 2H), 7.83 (m, 1H), 6.90 (dd, *J* = 8.4, 4.6 Hz, 1H), 6.84 (m, 1H), 6.78 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.58 (dd, *J* = 9.2, 3.0 Hz, 1H), 2.89-2.65 (m, 2H), 2.42 (m, 1H), 2.11 (m, 1H); IR (cm^{-1}): 3249 (N-H), 3025 (C-H aromatic ring), 2937 (C-H), 2832 (C-H), 1657 (C=O), 1439 (C=C), 1334 (C-H), 1309 (C-H), 1269 (C-N), 1118 (C-O), 1019 (C-F) cm^{-1}. Yield: 54%; mp 115-118 ^{o}C; MS (m/z): 407 (M+); Anal. calcd for $C_{18}H_{12}F_7NO_2$: C, 53.08; H, 2.97; F, 32.65; N, 3.44; O, 7.86; Found: C, 53.02; H, 2.86; F, 32.41; N, 3.38; O, 7.82.

BIOLOGICAL ACTIVITY

Pharmacology

The minimum inhibitory concentrations (MICs) of synthesized compounds were carried out by broth microdilution method as described by Rattan Antibacterial activity was screened against two gram positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two gram negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441) bacteria, ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323, Griseofulvin was used as a standard antifungal agent.

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and Mueller Hinton broth was used as nutrient media to grow and diluted the drug suspension for the test. Inoculum size for test strain was adjusted to 108 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used to dilute to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) were sub cultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted for obtaining 2000 µg/ml concentration, as a stock solution. In primary screening 500 µg/ml, 250µg/ml and 125 µg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml, 6.25 µg/ml, 3.12 µg/ml and 1.56 µg/ml concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC. Results obtained are given in Table 1.

Antibacterial Activity

The minimum inhibitory concentrations (MICs) of the tested compounds are shown in Table 1. The different compounds **3(a-j)** were tested for *in vitro* against two gram positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 443) and two gram negative (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441) bacteria. From the screening data, some of them possessed excellent antibacterial activity compared to ampicillin (MBC, 50-250 µg/ml) against gram positive *S. aureus.*

Compounds **3e** and **3i** showed MBC value in the range between 100-150 µg/ml against *S. aureus* while ampicillin has standard MBC value of 100 µg/ml against *S. aureus* which indicates that this compounds have excellent activity, while other compound **3f** possessed MBC value in the range of 200-250 µg/ml against against gram positive *S. aureus* compared with ampicillin. Compounds **3a** and **3g** have MBC of 100 µg/ml which was comparatively good against *S. pyogenus* while compounds **3d** and **3j** displayed moderate activity in the range of 200-250 µg/ml against *S. pyogenus* as compare to ampiciline. Compounds **3a, 3c** and **3h** showed MBC value in the range between 200-250 µg/ml against gram negative *E. coli* compare to ampiciline. Compounds **3c** and **3d** showed MBC value in the range between 100-150 µg/ml very good activity against *P. aeruginosa*, while compounds **3f** and **3i** displayed moderate activity in the range of 200-250 µg/ml. The remaining Chromene derivatives possessed moderate to poor activity against all four bacterial species.

Antifungal Activity

The minimum inhibitory concentrations (MICs) of the synthesized compounds are shown in Table 1. For *in vitro* antifungal activity, three fungal species *C, albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 were used and compared with standard drugs nystatin and greseofulvin. Most of the compounds possessed very good antifungal activity against *A. niger*; their MFC values were in the range between 100-500 µg/ml. Compounds **3a** and **3e** possesses good activity of 100-150 µg/ml against *C. albicans*, compounds **3b** and **3i** showed excellent activity of 100-250 µg/ml which is similar to griseofulvin (100 µg/ml) and nystatin (100 µg/ml) against *A. niger*, while compounds **3h** and **3j** possesses good activity of 100-250 µg/ml against *A. clavatus*. whereas remaining compounds possessed moderate to poor activity against *C. albicans* and *A. clavatus* compared with griseofulvin.

Table-1: *in vitro Antimicrobial Screening Results for PKG-101 to 110*

Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.aureus	***S.pyogenus***	***E.coli***	***P.aeruginosa***	***C.albicans***	***A.niger***	***A.clavatus***
3a	500	**100**	200	450	**150**	500	900
3b	450	900	500	500	900	**200**	>1000
3c	1000	450	250	**150**	550	900	450
3d	450	200	500	**62.5**	1000	>1000	>1000
3e	**100**	500	450	500	**100**	500	500
3f	250	450	450	250	450	>1000	1000
3g	900	**100**	450	900	>1000	550	900
3h	500	1000	200	450	500	500	**100**
3i	**150**	450	450	200	450	**150**	1000
3j	500	250	450	500	450	500	250
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

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